

e-MomCare: ReMote Monitoring in Pregnancy Care

– Progress Report version 2 for STITPRO –

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1 Motivation

The current high costs of healthcare and, in addition, the trend of increasing costs due to the ageing society, are important issues in the western world, and the Netherlands is no exception in this regard. This has put the current healthcare systems in the spotlights of the Dutch politicians, many of whom have concluded that it is not possible to continue in the current track. Thus, the implementation of measures for cost reduction is one of the most significant current trends in healthcare, and measures that are effective are really sought after. One way by means of which cost reduction can be achieved is by increasing the efficiency within healthcare organisations, e.g., by reduction of the number of “days in a hospital”, reduction of costly treatment programmes, and the number of face-to-face consultations. Another way is prevention by detecting people at risk in an early stage and providing guidance to prevent costly hospitalisation. It is also important to motivate people to maintain a healthy lifestyle. In the modern world, people are feeling increasingly responsible for their health, and many people, in particular when young, wish to be involved in the decision making associated with their health or disease. Measures taken to realise this have been referred to as *patient empowerment*. A particularly important measure is adapting general decision-making models to the individual’s characteristics, usually referred to as *personalisation*.

Personalisation of care can be applied in various forms ranging from a simple adjustment of a system’s settings to the user’s capabilities (e.g., volume level adjustment of a hearing aid tailored to the person’s hearing capabilities), to a variety of user interface options (e.g., tactile, voice), and to a more complex degree of system’s adaptation capturing the entire patient’s environment. Various e-Health systems for personalised patient monitoring have been proposed in the literature. In [1] the authors propose a medical embedded device for individualised care allowing adaptive sensor management and autonomous diagnostic inference based on probabilistic methods. To supervise a physical fitness activity, in [2] a wearable mobile personal trainer system is proposed, based on alternating jogging and fitness exercises in an open-air environment. An intelligent personal monitor is proposed in [3], where a committee of artificial neural networks is used to raise alarm for unwanted cardiac events.

In this report, we describe research that, in accordance with the developments described above, aims at providing decision support to women with pregnancy-related disorders. Women with

pregnancy-related disorders are unique for a number of reasons: (i) as their disorder is pregnancy related, the disorder will be ‘cured’ automatically after child birth; (ii) the patients are relative young in comparison to the majority of patients, who are older than 65 years; young patients have more interest in applying modern technology such as smart phones to the management of their disease; (iii) pregnant women have a strong wish to be actively involved in improving the health of both their child and their own and be informed, about relevant decisions made by healthcare professionals, in particular midwives and gynaecologists, during the course of their pregnancy. When the pregnancy is the cause of illness, such as is the case with *(pre)eclampsia*—a syndrome characterised by high blood pressure, or hypertension, and associated deterioration of renal and cardiovascular function—clinical intervention is needed to protect the lives and health of both mother and child. Thus, when there is a suspicion that the pregnant female will develop (pre)eclampsia, she becomes a patient who is monitored on a regular basis within the hospital by the gynaecologist. Yet, we believe that electronic, information and communication technologies, i.e. *e-Health*, can contribute to improving the quality of this care by offering person-centric devices that can provide feedback and decision support regarding the progression, or lack thereof, of the disease. Such decision support could in principle offer greater involvement and control of the patient on her disease.

It is the aim of the *e-MomCare project* to develop a prototype of such a decision-support system, the *e-MomCare system*, that is accessible to the patient using a personal computer or cell phone, with the, in principle, possibility to collect and exchange information between patient, measurement devices (e.g. blood pressure device), and the hospital information system. Novel in this research in comparison to existing electronic solutions, such as devices that collect and analyse physiological parameters and send them to a personal computer or cell phone for visualisation or for dispatching the patient data to a central data server, is that our work focuses on the development of a model that, based on the data available from different sources, will be able to *predict* evolution of the disorder, in our case (pre)eclampsia. Thus the decision support offered will be *intelligent*, which will allow replacing some of the feedback that a gynaecologist can offer by feedback from the decision-support system.

This report offers a summary of the work that has been done so far, and the results achieved. In addition, it includes an outlook into the future of our research.

2 Background to the Research

2.1 Patient Group

Approximately 15% of first-time pregnant women develop high blood pressure and approximately half of them develop associated problems, such as kidney damage and subsequent proteinuria (excretion of protein into urine), leading to the syndrome of *preeclampsia*. The latter often occurs after 20 weeks of pregnancy or immediately after the delivery. As a multisystem disorder, preeclampsia affects the placenta, and it can affect the mother’s kidney, liver, heart and brain. When preeclampsia causes epileptic seizures, the condition is known as *eclampsia*. Preeclampsia is the most important cause of death among pregnant women in The Netherlands and it is also a leading cause of fetal complications, which include low birth weight, premature birth, and still-birth. As a pregnancy-related condition the only way to cure preeclampsia is to deliver the baby through caesarean or induction. Only early anti-hypertensive treatment in the subclinical, mostly moderately hypertensive phase, reduces the risk on preeclampsia.

2.2 Classification: Signs and Symptoms

The National High Blood Pressure Education Program (NHBPEP) Working Group classifies hypertensive diseases in pregnancy into 4 groups as follows (‘BP’ stands for blood pressure’) [4]:

- Gestational hypertension

- BP of 140/90 mm Hg or greater for the first time during pregnancy
- No proteinuria
- BP returns to normal less than 12 weeks postpartum
- Final diagnosis made only postpartum
- Chronic hypertension
 - BP of 140/90 mm Hg or greater before pregnancy or diagnosed before 20 weeks gestation not attributable to gestational trophoblastic disease OR
 - Hypertension first diagnosed after 20 weeks gestation and persistent after 12 weeks postpartum.
- Preeclampsia/eclampsia
 - BP of 140/90 mm Hg or greater after 20 weeks gestation in a women with previously normal blood pressure and with proteinuria ($> 0.3\text{g}$ protein in 24-h urine specimen)
 - Eclampsia is defined as seizures (strokes) that cannot be attributable to other causes in a woman with preeclampsia
- Superimposed preeclampsia on chronic hypertension
 - New onset proteinuria ($> 300\text{mg}/24\text{ h}$) in a woman with hypertension but no proteinuria before 20 weeks gestation
 - A sudden increase in proteinuria or blood pressure, or platelet count less than 100,000 in women with hypertension and proteinuria before 20 weeks gestation

Furthermore, depending on its severity preeclampsia can be further classified as mild or severe. *Mild* preeclampsia is defined as systolic blood pressure (SBP) ≥ 140 mmHg and diastolic blood pressure (DBP) ≥ 90 mmHg, accompanied by $> 1+$ proteinuria. The majority of patients will only have mild disease, but an important, and largely unpredictable, subset will progress to the *severe* syndrome, which is defined by one of the following criteria:

- SBP ≥ 160 mmHg or DBP ≥ 110 mmHg
- Proteinuria of > 5.0 g on a 24-hour collection (3-4+ on dipstick)
- Thrombocytopenia (low platelet count) with elevated hepatic enzyme activities and/or evidence of microangiopathic hemolytic anemia (“HELLP” syndrome)
- Oliguria (very low urine output) less than $500\text{mL}/24$ hours and/or serum creatinine $> 106\mu\text{mol}/\text{L}$
- Signs of respiratory problems (pulmonary edema, bluish tint to the skin)
- Severe fetal growth restriction
- Stroke

In addition, HELLP syndrome (Hemolysis, Elevated Liver enzyme, Low Platelets) is a form of severe preeclampsia that has been associated with particularly high maternal and perinatal morbidity and mortality and may be present without hypertension or, in some occasions, without proteinuria.

Common symptoms accompanying preeclampsia are: swelling or edema (especially in the face (eyes) or hands), sudden weight gain, headache, nausea or vomiting, changes in vision, racing pulse, stomach pain.

The distinction between mild and severe preeclampsia is important because the management strategies are very different. In many cases, the symptoms will be monitored with regular laboratory tests, but in some cases patients need to be admitted to hospital.

2.3 Pathogenesis

In the recent years, more understanding in the pathogenesis of preeclampsia has been obtained. In a very recent work, a two-stage model for preeclampsia is proposed [5]. The first (placental) asymptomatic stage is marked by abnormal placentation, followed by placental elaboration of certain soluble factors that enter the maternal circulation and cause subsequent widespread endothelial dysfunction. The second (maternal) stage is characterised primarily by hypertension and proteinuria, the clinical picture known as the maternal syndrome. It has been recently hypothesised that an imbalance in circulating angiogenic factors may play a pathogenic role in preeclampsia.

Another study proposes a scheme for the pathogenesis of intrauterine growth restriction (IUGR) and preeclampsia [6]. The authors' hypothesis is that both women experiencing preeclampsia and IUGR enter pregnancy with some degree of endothelial dysfunction, a lesion that predisposes to shallow placentation. According to the study, preeclampsia develops when abnormal placentation interacts with maternal metabolic syndrome, comprised of adiposity, insulin resistance/hyperglycemia, hyperlipidemia, and coagulopathy. On the other hand, IUGR develops in the absence of antenatal metabolic syndrome. Among these women, the baby is affected by shallow placentation but the mother does not develop clinically apparent disease.

Discussion of the clinical spectrum of hypertension with focus on preeclampsia is given in [7]. The authors provide a thorough description of the multi-systemic pathophysiology (kidney, placenta, brain, liver and coagulation abnormalities) related to preeclampsia as well as discussion on the pathology, prediction, prevention and management of the disease.

Another very recent study provides a review on understanding the origins of the disease and a summary of the risk factors and clinical features [8]. The authors discuss extensively the pathogenesis mechanisms of preeclampsia, including abnormal placentation, altered angiogenic balance, maternal-fetal immunological intolerance and inflammation/oxidative stress (e.g., limited sperm exposure, change in paternity, conceiving in vitro).

Although there has been marked progress toward understanding its pathogenesis, few inroads have been made in the areas of prediction and management of preeclampsia.

3 Diagnosis and Prediction of Preeclampsia

3.1 Diagnosis

Hypertension is diagnosed when 2 blood pressure readings of 140/90 mm Hg or greater are noted 6 hours apart within a one-week period. When serial readings are obtained during an observational period, the higher values should be used to make the diagnosis. To diagnose proteinuria, a 24-hour urine collection for protein and creatinine should be obtained whenever possible. Up to 30% of women with gestational hypertension who have trace protein noted on random urine samples may have 300 mg of protein in a 24-hour urine collection. Thus, 24-hour urine protein analysis remains the criterion standard. Alternatively, greater than 1+ protein on a dipstick analysis on a random sample is sufficient to make the diagnosis of proteinuria. Random urine samples can be used to calculate the protein-creatinine ratio. Thresholds of 0.14 – 0.3 have been proposed for diagnosing proteinuria. However, the best threshold for identifying pregnant women with significant proteinuria has not been agreed upon. Up to 10% of patients with preeclampsia and 20% of patients with eclampsia may not have proteinuria [9].

Despite the rigorous classification outlined above, the timely diagnosis of preeclampsia is not a trivial task. On the one hand the stage in pregnancy when high blood pressure appears is variable and associated problems can develop within a few days. Furthermore, since the final diagnosis of gestational hypertension can only be made in retrospect, a clinician may be forced to treat some women with gestational hypertension as if she has preeclampsia. On the other hand, preeclampsia may not be noticeable to the woman who has it. If a woman has underlying renal or cardiovascular disease, the diagnosis of preeclampsia may not become clear until the disease becomes severe. This requires frequent outpatient controls leading to high pressure for the second-and third-line healthcare centres.

3.2 Laboratory Control

Currently, the health condition of a pregnant woman is monitored during regular outpatient visits, where a number of measurements are taken such as maternal blood pressure, heart rate and urine analysis. The fetal condition is monitored by assessment of the fetal heart rate and growth using Doppler ultrasound, for example. In addition, careful controls are carried out when the mother experience warning symptoms (headaches, upper abdominal pain, rapid weight increase) that are threatening for hypertensive complications.

All women who present with new-onset hypertension should have the following laboratory tests: serum alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT) levels, serum creatinine and uric acid, platelet count (blood clotting). While controversy exists over the threshold for elevated liver enzyme, the values of ASAT > 70 U/L and LDH > 600 U/L, proposed in [10] appear to be the most widely accepted. Alternatively, values that are 3 standard deviations away from the mean for each laboratory value may be used for ASAT. Other laboratory values suggestive of preeclampsia include elevation in hematocrit and a rise in serum creatinine and/or uric acid. While these laboratory abnormalities increase the suspicion for preeclampsia, none of these laboratory tests should be used to diagnose preeclampsia.

3.3 Prediction

Predicting the appearance of preeclampsia in an earlier stage of pregnancy would be of great value, as it would identify those women who are at increased risk of developing preeclampsia and require intensive monitoring, and allow intervention before life-threatening complications develop. It could further clarify the pathogenic mechanisms for development of preeclampsia and ultimately lead to better and more specific strategies for management and prevention of the disease.

As defined in [9] “prediction refers to the application of a test to asymptomatic people for the purpose of classifying them in respect to their likelihood of developing a particular disease at a later date”. In this respect preeclampsia is an appropriate disease to screen, as it is common, important, and responsible for the increases both maternal and perinatal mortality. The intensified monitoring of high-risk women could decrease the severity of maternal morbidity and might lower the incidence of adverse outcome for both mother and neonate.

Numerous screening tests for preeclampsia have been proposed over the past few decades. A screening test should be safe, valid, reliable, acceptable to the population, reproducible, appropriate for the population, and cost-effective. However, to date, no test has been shown to appropriately screen for preeclampsia [11].

In our current research we focus on predicting the chance of developing preeclampsia given the risk factors and the measurements of the patient in the early controls at 12 and 16 weeks. At this stage, early aberrations in blood pressure and hematocrit may indicate circulatory maladaptation which precedes preeclampsia at a later stage. Timely detection not only indicates those to be at closer surveillance, it also gives the opportunity to start preventive medication. Next we review the maternal risk factors, which play a crucial role in the risk for developing the syndrome.

3.3.1 Risk Factors

It is known that various risk factors have an impact on the likelihood of developing preeclampsia [12, 13]. In [14], the authors provide a systematic review of works studying the impact of various risk factors for preeclampsia. Based on this review and additional sources, below we outline the risk factors used in the current research.

- Pre-existing medical conditions
 1. **Antiphospholipid (APS) syndrome:** disorder of coagulation that causes blood clots (thrombosis) in both arteries and veins. It has extremely low incidence rate of only 0.03% but if occurs, it most likely leads to pregnancy-related complications (miscarriage, stillbirth, preterm delivery, or severe preeclampsia). The increased risk is 10-fold.

2. **History of preeclampsia:** women who had preeclampsia in their first pregnancy are likely to develop preeclampsia in the second pregnancy. The increased risk is 7-fold.
 3. **Chronic hypertension:** a history of high blood pressure before the pregnancy or at booking; increases the risk for vascular dysfunction and thus the risk for preeclampsia
 4. **Renal (kidney) disease:** a history of renal disease before the pregnancy or at booking; increases the risk for renal dysfunction and thus the risk for preeclampsia
 5. **Diabetes:** a history of diabetes before the pregnancy or at booking; increases the risk for renal and vascular dysfunction and thus the risk for preeclampsia. The increased risk is 4-fold.
- Genetics
 6. **Family history of preeclampsia:** women who have a mother, sister or both sister and mother with preeclampsia, have a higher chance for developing the syndrome. The increased risk is 3-fold. Also women who have a father born from a preclampsic pregnancy are at an increased risk but less than that for first-degree female relative.
 7. **Family history of hypertension:** predisposes to an increased preeclampsia risk and it also increases the chance of developing hypertension. The increased risk is 2-fold.
 8. **Family history of diabetes:** predisposes to an increased preeclampsia risk and it also increases the chance of developing diabetes. The increased risk is 2-fold.
 - Pregnancy characteristics
 9. **Parity:** woman who has never given live-birth is called *nulliparous* and it has 3-fold risk for preeclampsia. For parous women without a history of preeclampsia the risk is low.
 10. **Multiple gestation (pregnancy):** when a woman is pregnant with twins then her risk for preeclampsia increases 3-fold.
 - Maternal characteristics
 11. **Obesity:** it is measured by Body Mass Index (BMI)—a mathematical measurement, approximating the percentage of body fat by comparing a person’s weight and height and it is the most widely used tool to identify weight problems; defined as $\text{weight}/\text{height}^2$. If BMI is between 25 and 30, then the woman is *overweight* and if BMI is greater than 30 then she is *obese*. The increased risk for obese women is 2-fold.
 12. **Age:** the age of the patient at the time of pregnancy; it is considered that for every additional year of age past 34, the risk for preeclampsia increases with 30%. The increased risk is 2-fold.
 13. **Smoking:** smoking women are at a decreased risk for preeclampsia than non-smoking ones [15].

3.3.2 Related Research

A number of scientific works have dealt with the problem of predicting preeclampsia at different stages during pregnancy. Here we review some of the most recent research.

In [16] the authors investigate the performance of mean arterial pressure (MAP) at 11^{+0} to 13^{+6} weeks combined with patient’s medical history as a screening test for preeclampsia. A multivariate Gaussian model was fitted to the distribution of log multiple of the median (MoM) MAP in the preeclampsia and unaffected groups. Likelihood ratios for log multiple of the median MAP were computed and used together with maternal variables to produce patient-specific risks for each case. In the prediction of preeclampsia, significant contributions were provided by log MoM MAP, ethnic origin, body mass index, and personal history of preeclampsia. The detection rate of preeclampsia by log MoM MAP and maternal variables was 62.5% for a false-positive rate

of 10%. The authors conclude that maternal variables together with MAP at 11⁺⁰ to 13⁺⁶ weeks identify a group at high risk for development of preeclampsia. Furthermore, the mean MoM MAP at 11⁺⁰ to 13⁺⁶ weeks in those developing preeclampsia did not change significantly with gestation at delivery. So it is equally effective for screening at early and late disease.

The same authors have recently conducted a similar study, presented in [17]. They used logistic regression analysis on a combination of maternal factors and pregnancy-specific markers, such as uterine artery pulsatility index, pregnancy-associated plasma protein-A, and placental growth factor in early pregnancy to provide first-trimester prediction of hypertensive disorders. A large database of 7797 singleton pregnancies, from which 96.3% were unaffected by preeclampsia or gestational hypertension, has been used for building and evaluating the model. The results obtained were very encouraging: the proposed methodology was able to detect 93.1% of early preeclampsia and 35.7% of late preeclampsia at a 5% false-positive rate. In addition, 20% of the pregnancies classified as screen positive turned out to develop pregnancy hypertension.

In [18] it is investigated whether first-trimester arterial pulse wave analysis (PWA) can predict preeclampsia in 210 low-risk women with a singleton pregnancy. Pulse wave analysis is a simple procedure, which allows the evaluation of the functional integrity of the blood circulation. Although this technique has been discovered more than hundred fifty years ago, physicians dealing with hypertension have paid little interest to it and are content to measure just the highest (systolic) and lowest (diastolic) value of the brachial pressure pulse in diagnosing and treating this condition. In [18], using logistic regression models, the authors showed that first-trimester arterial PWA can play a significant role in understanding the pathophysiology of the disease and has a potential for early screening purposes.

More advanced marker is studied in [19] where the authors evaluate whether first trimester maternal serum placental protein 13 (PP13) can predict preeclampsia among women with a priori high risk. They use MoMs PP13 levels, which showed better prediction results for early-onset preeclampsia (< 34 weeks) than for late-onset disease.

Another very recent study on first-trimester prediction of preeclampsia for high-risk women is presented in [20]. The study used an earlier developed logistic regression model for low-risk pregnancies and a combination of maternal factors, where at least one high-risk condition was present, and mean uterine artery pulsatility index at 11⁺⁰ to 13⁺⁶ weeks to distinguish between the groups of unaffected, late and early preeclampsia risks. The results on a dataset of 152 high-risk pregnancies (84.8% unaffected) showed modest performance of the model: detection rates of 23.1% and 42.9% for late and early preeclampsia at 10% false-positive detection rates. Several reasons might be for this outcome. First it is likely that different logistic regression models, i.e., different parameters, are better suited for high-risk and low-risk pregnancies than one combined one. Second using the high-risk condition(s) in the prediction model might also improve the prediction results than just to select the patients. Finally, as the authors also pointed out in the discussion section, for high-risk women, the predisposing maternal factors may become more important and obscure early observation of impaired organ function, which is also due to hypertensive pregnancy-related disorders.

Nijdam et. al have developed a logistic regression model to discriminate between low-risk and high-risk pregnancies for initially normotensive and nulliparous women based on three clinical variables obtained at the antenatal booking: systolic and diastolic blood pressure, and weight [21]. The authors used two datasets provided by two Dutch hospitals to construct and evaluate the model. To obtain more reliable validation, bootstrapping and split sample (train on the one dataset and test on the other) analysis were applied. The results demonstrated certain capability (AUC = 0.78) of the proposed methodology to identify correctly very low-risk and very high-risk women of becoming hypertensive before 36 weeks of pregnancy.

A detailed overview of previous work on developing prediction tests is given in [22].

4 Alternative Approach: Remote Monitoring

Although the patient data for the aforementioned risk group of pregnant women is currently determined in the outpatient clinic, requiring the patient to come to the hospital, large amount of these data can also be collected at home and automatically sent to the healthcare team. The measurements taken at home environment have the advantage of being more representative than the values found in the clinic. Moreover, there will be no need for the patient to visit frequently the hospital and she can be actively involved in her own medical care. Finally, the remote monitoring can contribute to reducing the working pressure on midwifery care, and possibly to cost savings in healthcare.

We consider electronic home monitoring of risk patients via the Internet, so that patient data is automatically available for the care team. This should reduce significantly the frequency of outpatient control while ensuring comparable or even improved level of healthcare. This form of home monitoring requires an intelligent system on the clinical side, while security must be ensured. The electronic healthcare system should be intelligent, because it is desirable that both doctor and patient get an insight in the patient's health status and need for care without additional efforts, such as frequent telephone contacts.

Given the cause-effect relationships and the uncertainty inherent in the medical domain, we suggest Bayesian networks as appropriate technique to construct a decision model for predicting preeclampsia. This model would make a statement about the progression of the disease based on the physiological measurements of the patient and to inform the patient and the care team whether or not an action should be taken. The development of the Bayesian model is a part of the current research work, because such model does not exist yet. In addition, the patient can get a graphical insight how her pregnancy develops in comparison to a reference group. This we would show by means of international fixed values, compared to a reference group adjusted for gestational age and compared to the expected course based on the baseline early in patient's pregnancy.

The electronic intelligent healthcare system will make use of an internet connection and it will consist of a number of modules, such as:

- *Software for automatic reading* of measurement equipment such as electronic blood pressure meter and a urine analyser, and possibly in a later stage, data measuring the status of the fetus.
- *Bayesian network decision model* which interprets the patient data and makes a prediction for the progression of the disease.
- *Web-application for communicating the results*, both textually and visually, to the care team and the patient and the data should be stored in a central database in the hospital.

We have opted for a smart phone as the development platform, as it offers certain advantages in comparison to an Internet-attached PC. In particular, the fact that the patients is wearing the smart phone and has access to its functionality anywhere and anytime is seen as an advantage. It is also much more effective to implement reminder functions on a smart phone than on a personal computer. Whereas a PC is normally switched off, a smart phone is usually not, and will thus allow reminding the patient of the need of taking measurements at any time during the day. When opting for a smart phone solution, the resulting interaction between the system's modules and the user is schematically presented in Figure 1.

5 Bayesian Network Model for Predicting Preeclampsia

5.1 Bayesian Networks and Causal Independence Models

A *Bayesian network* is defined as a pair $BN = (G, P)$, where G is an acyclic directed graph (ADG) $G = (V, E)$ and P is a joint probability distribution of the random variables X . There exists a 1-1 correspondence between the nodes in V and the random variables in X ; the (directed) edges, or

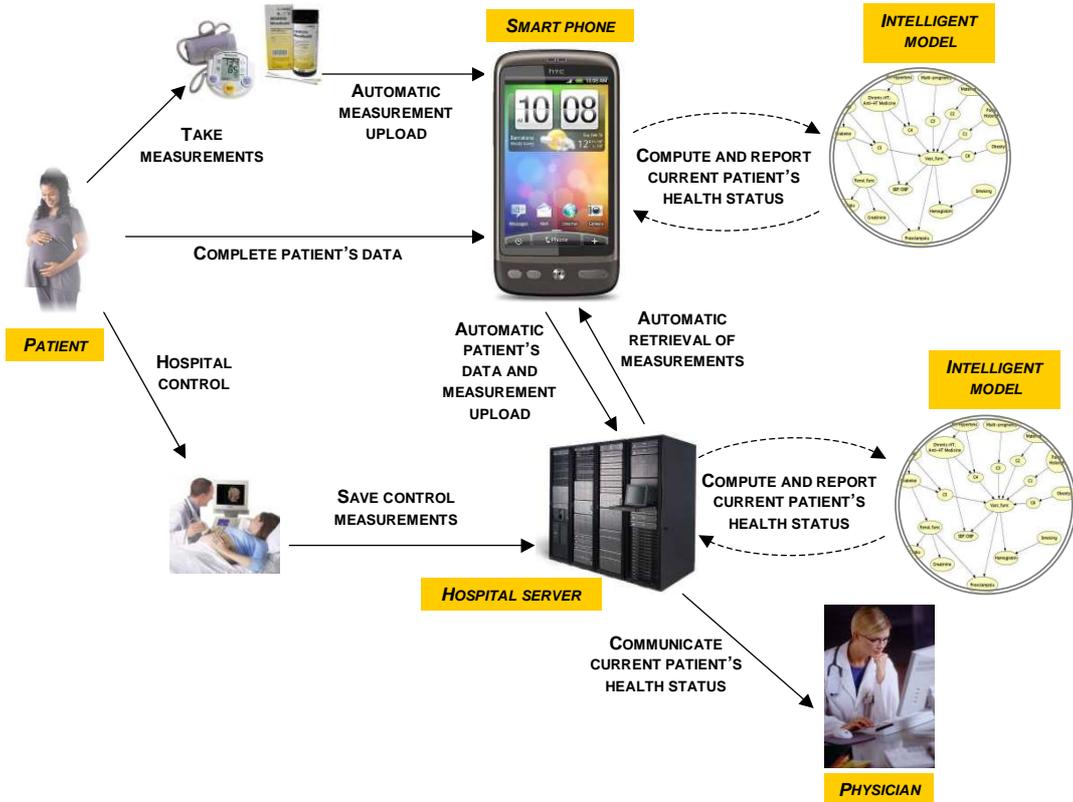


Figure 1: Schematic representation of the module and user interactions in the electronic intelligent healthcare system for pregnancy care.

arcs, $E \subseteq (V \times V)$ correspond to direct causal relationships between the variables. We say that G is an I -map of P if any independence represented in G , denoted by $A \perp\!\!\!\perp_G B \mid C$, with $A, B, C \subseteq V$ mutually disjoint sets of nodes, is satisfied by P , i.e.,

$$A \perp\!\!\!\perp_G B \mid C \implies X_A \perp\!\!\!\perp_P X_B \mid X_C ,$$

where A, B and C are sets of nodes of the ADG G and X_A, X_B and X_C are the corresponding sets of random variables, indexed by A, B , and C . The acyclic directed graphical part of a Bayesian network G is by definition an I -map of the associated joint probability distribution P . A Bayesian network BN offers a compact representation of the joint probability distribution P in terms of local *conditional probability distributions* (CPDs), by taking into account the conditional independences represented by the ADG.

Determining the CPDs a priori or in a learning process might be a cumbersome task if a large number of variables or complex relationships are present, which is often the case in practice. Even when knowledge about every parent-child relationships is available, it might still be prohibitive to define the probability table for the combined effect of all parent nodes on the child due to the large number of parent combinations. From the Bayesian network definition it is clear that the size of a probability table of the child node is exponential in the number of parents. To provide an efficient way to specify interactions among random variables in a compact fashion, the notion of *causal independence* has been introduced [23]. Causal independence arises when multiple causes (parent nodes) lead to a common effect (child node) through interaction of independent uncertain processes. This type of models allows in a systematic way to decompose a probability distribution in terms of Boolean interactions among local parameters. Such a decomposition makes it easier and tractable to deal with problems involving a large number of causes, which is often the case in

many domains such as medicine.

A definition of the notion of causal independence is given following the one from [24]. The general structure of a causal-independence model is shown in Figure 2. It expresses the idea that causes C_1, \dots, C_n influence a given common effect E through intermediate variables I_1, \dots, I_n ; the intermediate variable I_j is considered to be a contribution of the cause variable C_j to the common effect E . The *interaction function* f represents in which way the intermediate effects I_j , and indirectly also the causes C_j , interact. This function f is defined in such way that when a relationship between the I_j 's and $E = 1$ is satisfied, then it holds that $f(I_1, \dots, I_n) = 1(\text{true})$; otherwise, it holds that $f(I_1, \dots, I_n) = 0$. Note that each variable I_j is only dependent on its associated cause C_j and the effect variable E . Furthermore, the graph structure expresses that the effect variable E is conditionally independent of each cause C_j given the associated intermediate variable I_j . It is assumed that absent causes do not contribute to the effect, i.e., $P(I_j = 1 \mid C_j = 0) = 0$.

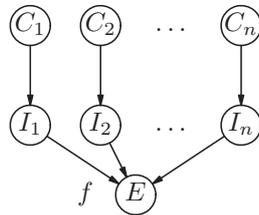


Figure 2: Causal-independence model

5.2 Modelling Scheme

5.2.1 Conceptual Framework

State model Before presenting the Bayesian network model for predicting preeclampsia, we first discuss the general conceptual framework about the development of a syndrome (disease). In medicine, a *syndrome* is defined as a set of associated symptoms, signs or conditions; see, for example, Section 2.2 for the classification of various pregnancy-related complications. These conditions are indicators for the dysfunction of one or more body organs and can be distinguished as major and minor in establishing the diagnosis of the syndrome. While the syndrome and the associated conditions may be correlated, however, they do not need to have a direct cause and effect relationship and it is possible that a separate underlying problem or risk factor explains the association. For example, the patient’s conditions such as existing diseases, age, gender, and genetics, affect the functioning of the organs related to the syndrome, which in turn has an influence on the corresponding laboratory measurements. Apart from the risk factors, the intake of medicine also affects the status of organ functioning aiming to reduce the risks or further development of complications. The schematic representation of these relationships is depicted in Figure 3, where the arrows indicate the cause-effect direction.

Note that the representation in Figure 3 is a fixed state of the body functioning at a particular moment when measurements are made or symptoms are detected. While such a “snapshot” of the body system might help for diagnosis purposes, it is definitely insufficient for prediction tasks. For the latter, observing the organs’ functioning over time is a necessity in order to establish trends and make plausible predictions about the potential development of a syndrome. Next we discuss the temporal extension of this state model.

Temporal model The health monitoring of a patient usually includes a number of controls made at different time points $1, \dots, T$. As we saw in the state model, the functioning of a particular organ X at a specific moment t , which is influenced by the medicine taken, determines the laboratory tests made then. However, taking into account the functioning of X at the previous control $t - 1$, allows the medical practitioners to observe whether or not big changes in the functioning occur and

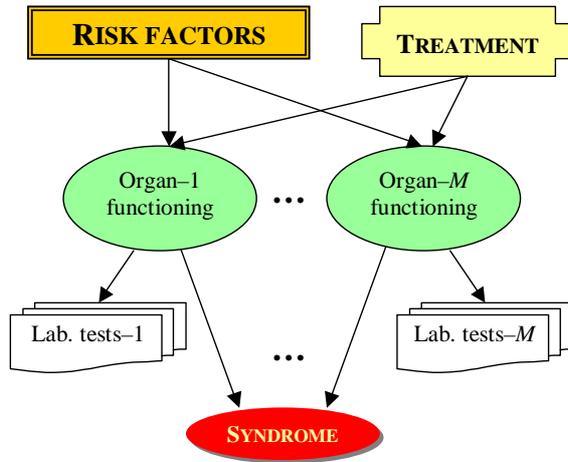


Figure 3: State model for the development of a syndrome

subsequently to establish a diagnose for the syndrome at moment t and if necessary, prescribe new or adjust the medication taken. Furthermore, given the history and the current status, one can make a step further and also make a prediction for the organ functioning and respectively for the development of the syndrome at next control time point $t + 1$. This chain process of dependencies between the subsequent controls is depicted in Figure 4. We followed this modelling procedure in developing the model presented next.

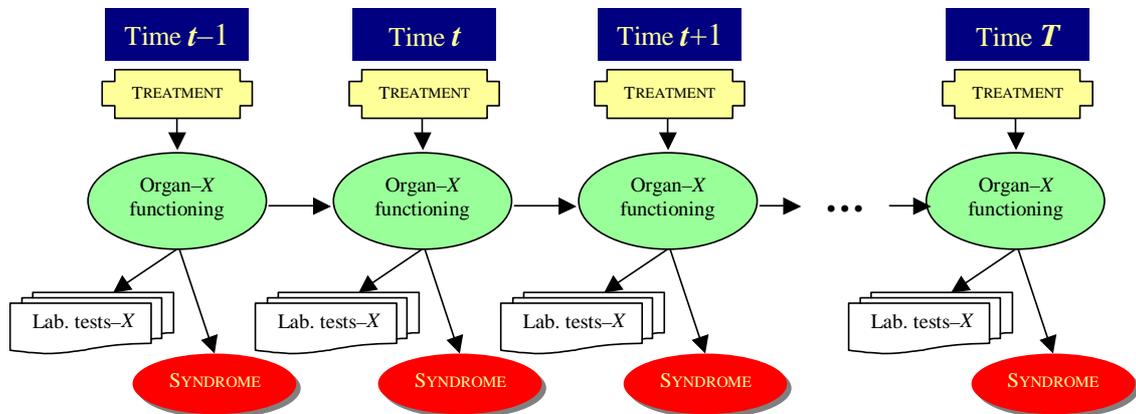


Figure 4: Temporal model for the functioning of a particular organ over a number of control time points

5.2.2 Bayesian Network Model

The initial model we develop is based on the risk factors described in Section 3.3.1, and laboratory measurements described in Section 3.2 and taken during 10 checkups at 12, 16, 20, 24, 28, 32, 36, 38, 40 and 42 weeks of pregnancy. The list of all factors and measurements with their set of values and abbreviated names as used in our model are given in Table 1. Note that the risk factors “Parity” and “History of PE” are combined as only parous women can have a history of preeclampsia. Then we explain and motivate the structure of the model.

The causal model is depicted in Figure 5. As discussed earlier the set of risk factors as defined

Table 1: Factors with their values and abbreviated names as used in the Bayesian network model.

Type	Factor	Abbreviation	Values / Ranges
Risk factors	Antiphospholipid syndrome	APS SYNDROME	no, yes
	Parity and History of preeclampsia	PARITY-HISTORYPE	nulliparous, parous=yes, parous=no
	Chronic hypertension	CHRONIC HT	no, yes
	Renal disease	RENALDISEASE	no, yes
	Diabetes	DIABETES	no, yes
	Drugs for Chronic hypertension	TREATMENT-CHT	no, yes
	Drugs for Renal disease	TREATMENT-RD	no, yes
	Drugs for Diabetes	TREATMENT-DB	no, yes
	Family history of preeclampsia	FH-PE	no, fatherPEpreg, mother-sister
	Family history of hypertension	FH-HT	no, yes
	Family history of diabetes	FH-DIAB	no, yes
	Multiple pregnancy	MULTI-PREGNANCY	no, yes
	Obesity	OBESITY	normal, overweight, obese
	Maternal age	AGE	< 20, 21-25, . . . , > 40
Smoking	SMOKING	no, yes	
Lab. tests	Systolic blood pressure (mmHg)	SBP	< 109, 110-119, . . . , 160-169, > 170
	Diastolic blood pressure (mmHg)	DBP	< 59, 60-69, . . . , 100-109, > 110
	Hemoglobin (mmol/L)	HB	6.2, 6.3, . . . , 9.3
	Creatinine ($\mu\text{mol/L}$)	CREAT	< 45, . . . , 118-121, > 122
	Protein (Albumin) – Creatinine ratio	PA/C	0-0.03, 0.04-0.06, . . . , 4.5-5, > 5
Extern.	Drugs taken by the patient	TREATMENT	no, Anti-HT, Other, Anti-HT+Other
Hidden	Vascular risk	VASC RISK	false, true
	Vascular function	VASC FUNC	ok, nok
	Renal function	RENAL FUNC	ok, nok
Syindr.	Preeclampsia	PE	no, yes

here determines the prior risk for preeclampsia. In particular, these factors have an impact on the functioning of the vascular system and hence, they determine the risk for vascular dysfunction, which for brevity we referred as to *vascular risk* and in our model it is represented by the non-measured variable VASC RISK.

In the current Bayesian network model, these cause-effect relationships would be represented by $\text{RISKFACTOR} \rightarrow \text{VASC RISK}$ structure. Then to define the CPT of VASC RISK given all possible combinations of risk factor values, we need to fill in a table with 165888 entries, which is practically impossible. Therefore to represent in a compact fashion this probability distribution, we use the causal independence models, described in Section 5.1. More precisely, we add the intermediate (hidden, non-observed) variables C_i , $i = 1, \dots, 9$ in order to model the interaction between the risk factors and the vascular risk. Note that the variables related to the three disorders—chronic hypertension, diabetes and renal disease— influence the vascular risk through a combined effect, represented by one hidden variable for each of them. Since, by domain knowledge the risk factors interact by adding up to the vascular risk, we choose naturally the logical OR as a function for representing this interaction in VASC RISK; this implies that if at least one of the risk factors is present then the vascular risk is true. This causal independence representation of the CPT of VASC RISK required only 39 entries to be estimated.

Given the definition of preeclampsia in Section 2.2, we consider the renal and vascular functioning as major conditions determining the syndrome. In our modelling scheme these functions are represented as two binary variables with values of *ok* and *nok* (not ok), indicating the respective function status. Note that these variables are more abstract and they do not have a direct measurement. However, as discussed earlier, several laboratory tests are performed at every control in order to determine the current health status, including the renal and vascular function, of the patient. The most common and easily made measurements are systolic and diastolic blood pressure reflecting the status of the vascular function and haemoglobin, serum creatinine and protein (albumin) to creatinine ratio reflecting the status of the renal function. In addition, the values of these measurements are explained by the presence of certain risk factors; for example

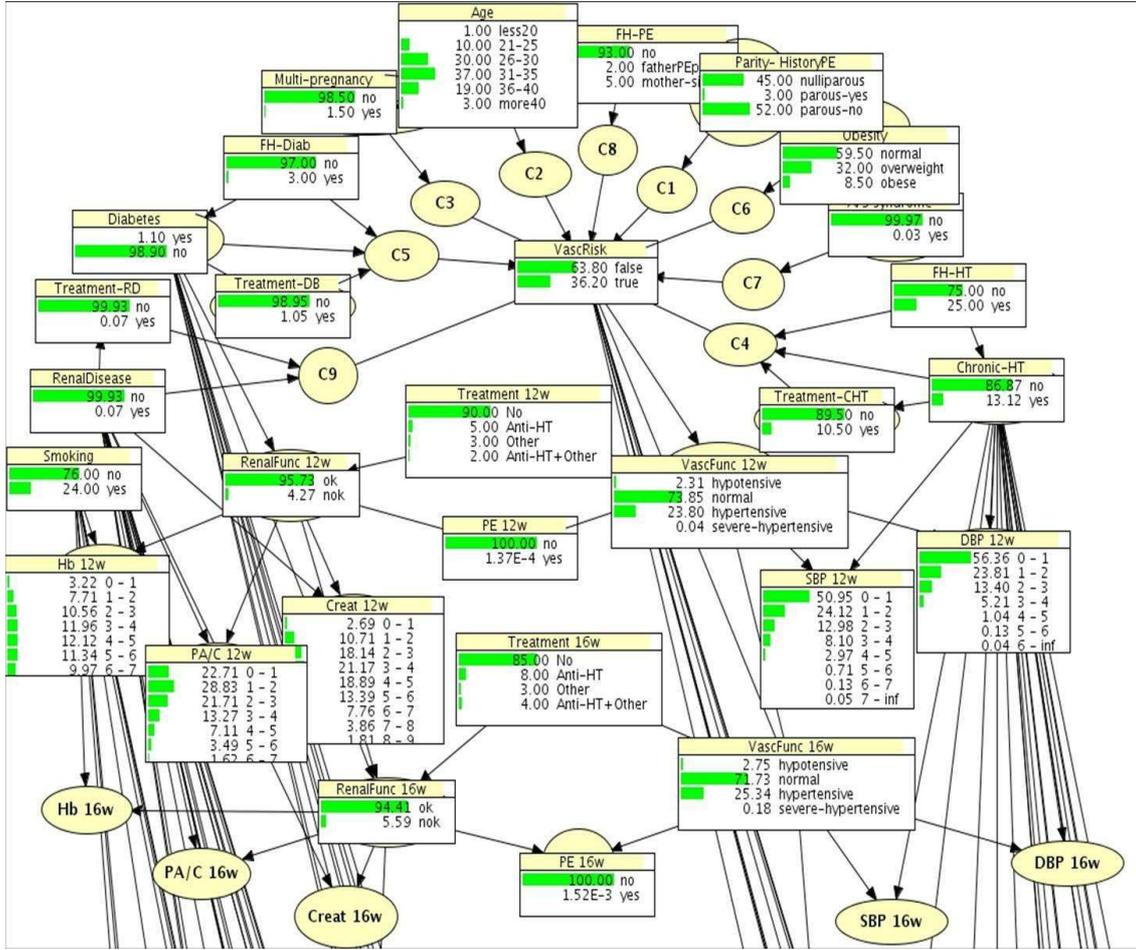


Figure 5: Part of the temporal Bayesian network model for preeclampsia with prior probabilities.

chronic hypertension affects the blood pressure values, renal disease has an impact on the values of creatinine and protein (albumin) to creatinine ratio, and smoking usually increases the level of hemoglobin. Except the laboratory measurements, however, any medicine taken by the patient at the time of the control, has an impact on the status of the renal and vascular function, which is captured by MEDICINE \rightarrow FUNCTION structure.

To capture the temporal development of both renal and vascular functions, we created a temporal model by adding links between the respective functional status at successive week checkups, following the representation in Fig. 4. As a result, the combined status of the renal and vascular function define the development of the syndrome of preeclampsia at each medical checkups. This modelling scheme allows determining the probability for preeclampsia at different stages.

Next to the structure of the Bayesian network model, we need to estimate the prior probabilities for the variables included. For the risk factors, we used the incidence rates and literature studies mentioned in Section 3.3.1. For the measurements we used expert knowledge and the sources discussed in Section 3.2. The prior probabilities are shown on Figure 5.

5.2.3 Preliminary Model Evaluation

We performed a preliminary analysis of the prediction performance of the model using data of actual patients. Table 2 includes clinical and laboratory data for up to 24 week checkups for one patient with and one patient without preeclampsia (PE), including the prediction for preeclampsia

Table 2: Input and output data for one patient with and one patient without preeclampsia.

Risk factors	Patient A: Not-preeclamptic				Patient B: Preeclamptic			
Age	26-30				36-40			
Smoking	yes				yes			
Obese	obese				normal			
Chronic HT	yes				no			
Parity-HistoryPE	parous=yes				parous=yes			
Per control	12 wk	16wk	20wk	24wk	12 wk	16wk	20wk	24wk
Treatment	Other	Other	Other	Other	Other	Other	Other	n/a
Systolic BP	127-129	118-120	121-123	121-123	124-126	118-120	118-120	136-138
Diastolic BP	76-79	68-71	72-75	76-79	64-67	72-75	64-67	80-83
Hemoglobin	n/a	6.7	n/a	6.2	7.5	n/a	7.4	7.4
Creatinine	n/a	58-61	n/a	46-49	50-53	n/a	n/a	62-65
Protein/Creatinine	n/a	0	n/a	0	0	n/a	n/a	0.3-0.6
$P_{PRIOR}(PE)$	0.0014	0.0076	0.05	0.16	0.0013	0.007	0.05	0.15
$P_{CURR}(PE)$	0.003	0.008	0.08	0.18	0.003	0.04	0.19	0.89
<i>Rel. change</i>	1.23	0.11	0.60	0.13	1.36	4.71	2.80	4.93

computed by the model. To facilitate the analysis of the results we added the relative change of the current risk $P_{CURR}(PE)$ with respect to the prior $P_{PRIOR}(PE)$ computed as $(P_{CURR}(PE) - P_{PRIOR}(PE))/P_{PRIOR}(PE)$, used also by the clinicians in evaluating the patient’s status. It is clear that for the preeclamptic patient the risk increases almost up to 5 times with respect to her prior risk in very early pregnancy, whereas for the non-preeclamptic patient the risk remains comparable over the pregnancy duration.

We next used data of 417 pregnant patients, of whom 33 ($\pm 7.9\%$) were preeclamptic, to evaluate to what extent the model is capable of distinguishing between the two groups of patients. In particular, we looked at cases with an increased relative risk change ≥ 1 with respect to the prior at a particular time point; the results are reported in Table 3. We considered a relative risk change larger than 1 as suspicious patient’s condition for the development of PE, requiring more regular monitoring.

Table 3: Number (%) of patients selected at a particular time with a relative change of risk ≥ 1 .

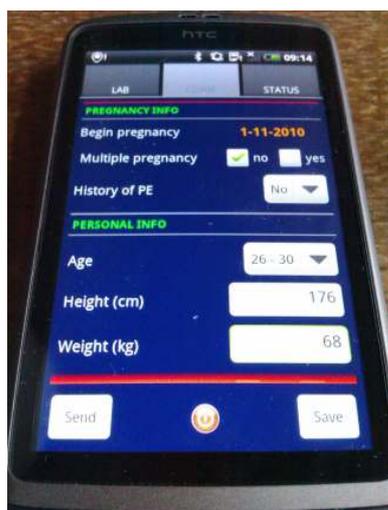
Time	PE patients	non-PE patients	Total
12 week	27 (82%)	207 (54%)	234 (56%)
16 week	24 (73%)	149 (39%)	173 (41%)
20 week	21 (64%)	144 (38%)	165 (40%)
Whole pregnancy	31 (94%)	247 (64%)	278 (67%)

At 12 weeks the model is able to detect 82% of the preeclamptic patients as suspicious, whereas almost half of the non-preeclamptic patients are judged as being non-suspicious. This is a desired result in patient monitoring where at an early stage a large part of the normal cases would not require intensive checkups thus reducing the workload of the physician and the number of visits to the out-patient clinic by patients. In addition, we considered the whole pregnancy duration as an

alternative to the weekly selection period to allow future risk changes to be taken into account as well. Then the model is capable of detecting a higher number of preeclamptic patients but at the cost of increased inclusion of a number of normal cases as being preeclamptic. We note that these results are preliminary as the collected data was not fully representative—the clinical information and laboratory measurements were not consistently recorded. For example, we lacked proper treatment information and for some of the preeclamptic patients blood pressure measurements were missing. We are currently collecting more data, which will be used to gain further insight in the model’s performance.

6 Implementation of the e-MomCare System

Implementation of part of the system using Google’s open source *android* operating system is currently developed. The Bayesian network model was built with the publicly available java-based Bayesian network package EBayes [25], which provides platform-independent engine for performing inference given evidence in the Bayesian network. The java version of the network was subsequently embedded in the android application. Although we are still investigating the appropriate design concerning the user interface and communication capabilities of the smart phone, in Fig. 6 and 7 we present some of the main components of the system to give a general impression of its usability.



(a) Clinic data



(b) Lab data: Blood pressure via Bluetooth



(c) Lab data: Protein (Albumin)–Creatinine ratio via urine test strips



Figure 6: Snapshots of the system *input* interface of clinic and lab data on android smart phone

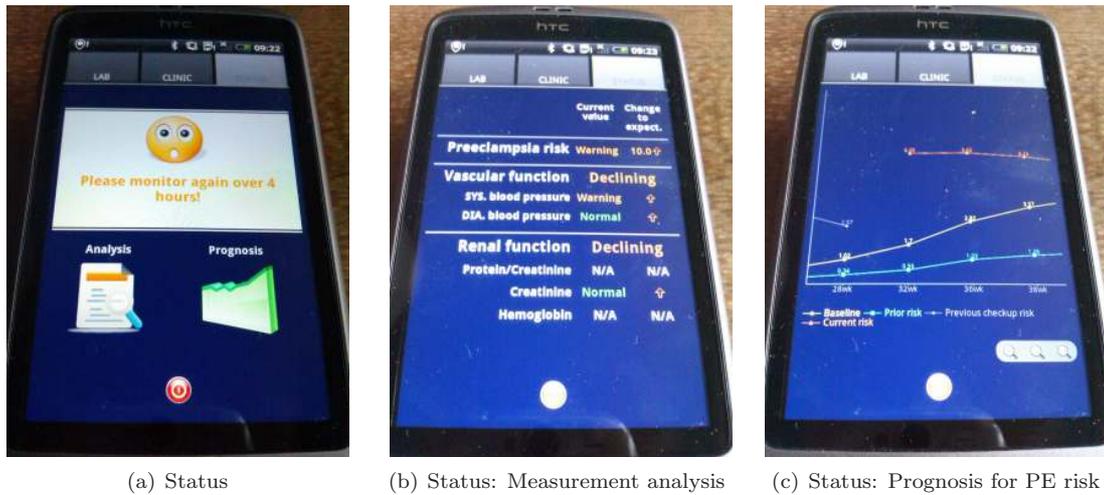


Figure 7: Snapshots of the system *output* interface on android smart phone

The interface on the smart phone comprises 3 main screens– 2 for input and 1 for output. The first input screen (‘CLINIC’ tab) concerns clinical information about the pregnant woman such as age, family or personal history of hypertension, diabetes etc. which is mostly likely to be inserted once at the beginning of the pregnancy. Later updates are, of course, also possible. This information is saved in a local database on the smart phone and the prior risk for developing preeclampsia during the pregnancy is automatically computed using the temporal Bayesian network model and the specific clinical information. The second input screen (‘LAB’ tab) is used to obtain the measurements made at home on regular basis. In the current version, we have developed (i) a module for the input of the blood pressure measurements obtained via a Bluetooth connection from a measuring device and (ii) a module for automatic analysis of urine test strips using the camera phone and imaging techniques allowing the measurement of albumin, protein and creatinine. The measurement data can be saved in the local database and submitted to the hospital server. The blood pressure device currently chosen is UA-767PBT Bluetooth by the Japanese A&D company with an inflatable upper arm cuff, to be suitable to measure blood pressure reliably. The urine test strips used are Microalbustix (albumin and creatinine) x 25 strips and Albustix (protein) x 50 strips by Siemens Healthcare, which have been tested for clinical use.

The output screen (‘STATUS’ tab) provides the pregnant woman with evaluation of her current health condition status based on her latest and previous checkup measurements. The status result is a combination of (i) the change in the probability for preeclampsia at the particular checkup in comparison to the prior risk, (ii) the current absolute value of the measurements and (iii) the difference between the expected measurements’ values computed by the Bayesian network model and the actual measurement value. The status is currently displayed as a ‘smiley’ whose colour indicates the prior risk of the pregnant woman and the emotion indicates the current risk. Next to the status a simple action recommendation is also provided. This output is, however, very simplified and as discussed in the introduction of this report, pregnant women wish to be informed about the decisions taken concerning their health status. To get insight in the status provided by their “personal intelligent health assistant”, the output interface is extended with (i) a screen displaying the status of the vascular and renal functions given the current measurements (‘Analysis’ button) and (ii) a screen with a chart plotting the risk of development of PE till the end of the pregnancy as computed by the Bayesian network model (‘Prognosis’ button).

The working principles of the smart phone interface are demonstrated in the following video: <http://www.youtube.com/watch?v=nulyaBA7mfc>

7 Project Status and Outlook

At the current stage of development (June, 2011), we have built:

- The Bayesian network model has been refined to include measurements over 10 checkup weeks during the whole pregnancy
- Java-based Bayesian network software has been ported to android, allowing local inference on the smart phone
- Module for a communication between a blood pressure device and the smart phone via Bluetooth
- Module for automatic analysis of urine test strips (albumin, protein and creatinine) using the camera phone and imaging techniques
- A first preliminary test with incomplete data of approx. 500 patients

The remaining tasks on the project include:

- Evaluation of the Bayesian network model with complete patient data and potential model refinement. One of the current bottlenecks is extraction of the data from the hospital information system, which within the organisation of UMCN St.Radboud requires a huge administrative overhead causing significant delay. However, such data are also collected as part of the research by clinicians within the hospital, and we have been able to profit from that synergy so far.
- Evaluation of the automatic urine strips analysis provided by the smart phone using laboratory samples.
- Development of a web-server for uploading patient information, simulating the hospital environment. Despite the developed digipoli system in UMCN St.Radboud, it is not yet available for the Department of Obstetrics and Gynaecology. Therefore, for the current project we are designing a communication infrastructure to an external web-server, playing a role of a hospital information system, to communicate patient-entered information in the home environment.
- Finalisation of the first prototype system and its evaluation with a patient group. Tests with midwives are being set-up to provide first feedback on the smart phone interface and the main features of the system.
- Investigation of the possibilities to reduce the size of the blood pressure device. Considering the small size of the smart phone, together with experts from the TechnoCentrum, Radboud University Nijmegen, we are investigating the minimal size of a functioning blood pressure device by removing for example the interface, using a smaller pump and number of batteries.

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