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Who's at risk?

van der Tuuk, Karin

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CHAPTER 09

DISCUSSION AND FUTURE PERSPECTIVE

DISCUSSION AND FUTURE PERSPECTIVE

This thesis focused on developing prediction models to guide obstetricians in the care of an individual patient with hypertensive disorders during pregnancy at term. These disorders are still a major cause of maternal and neonatal morbidity and mortality in the Netherlands, with a Maternal Mortality Ratio (MMR, maternal mortality per 100,000 live-born children) of 1.4 in the period 2006-2010.¹ Therefore, prevention of these adverse outcomes is of utmost importance. Uncertainty about the best management of these women resulted in the HYPITAT trial; a nationwide multicenter randomized controlled, open label trial, performed in the Netherlands between October 2005 and March 2008. The study compared induction of labour with expectant monitoring in pregnant women with hypertensive disease at term and concluded that induction of labour is the management of choice.² The HYPITAT study provided overall guidance for the management of women with hypertensive disease at term, but it is questionable whether induction is the best choice for every individual woman. This may depend on the probability that her condition progresses to a high risk situation or not, as well as the probability of other adverse outcomes. The individual risk profile for these outcomes may depend on individual characteristics, which can be difficult to take into account in decision making in clinical practice.

Decisions regarding interventions (*e.g.* induction of labour, caesarean section) are made based on the physician's assessment of the balance between the risks of expectant management versus those associated with a specific intervention. This assessment, however, is a complex, partly intuitive, and non-standardized process based on textbook knowledge, evidence from the literature and clinical experience, and estimates of average outcomes rather than individual outcome probabilities. We wanted to improve this situation by evaluating whether the risk of various outcomes that are relevant in women with gestational hypertension (GH) or mild preeclampsia (PE) at term could be assessed more individually by developing prediction models for specific maternal and neonatal outcomes (**Part 1**). Furthermore, we analyzed the influence of cervix favorability and blood pressure patterns on the outcome of pregnancy. In addition, we evaluated the impact of the HYPITAT trial in clinical practice in the Netherlands. We wanted to determine whether performing a nationwide multicenter trial initiated by the Dutch Consortium had an impact on the implementation of its recommendations on local, regional and national level, resulting in new guidelines and subsequent improved maternal health (**Part 2**).

PART 1: CLINICAL PREDICTION MODELS.

Over the years more and more prediction models have been developed, but relatively little progress has been made in predicting which women will progress to severe disease or will develop other maternal morbidity. In this thesis several variables are identified in women with GH or mild PE at term which predict an increased risk for specific maternal morbidity, such as progression to severe disease (**chapter**

2), postpartum hemorrhage (**chapter 3**), adverse neonatal outcome (**chapter 4**) and caesarean section (**chapter 5**). Using clinical characteristics and biochemical/hematological parameters we were able to construct models predicting the individual risk of these specific outcomes. The discrimination and goodness of fit is not optimal in all prediction models, but a distinction between low and high risk of developing a specific outcome could be made. Further research will demonstrate whether these models hold at external validation and can serve to guide clinical management.

Developing a clinical prediction model consists of a number of steps, *i.e.* development, internal- and external validation and analysis of its clinical impact. The four models in this thesis were developed up to the stage of internal validation, according to best practice and expert opinion at the time the work was carried out. This involved multiple imputation of missing data and using risk estimates from logistic regression analysis pooled across the imputed datasets. We included variables according to the Akaike information criterion, except for the progression to a high risk situation model where we chose to include all variables with a P-value ≤ 0.40 . No consensus existed on the best method for selecting variables, there are multiple options. One is the full model approach in which all potentially relevant variables are included irrespective of their univariate influence on the outcome. This should avoid overfitting and selection bias and provide correct P-values and standard errors.³ A second method uses backward selection of all potentially relevant variables or from a specific significance level, as we did in our analysis. The choice of a specific significance level had a major effect on the number of variables selected.⁴ In the other three chapters we used a threshold based on the Akaike information criterion, including the variables with a P-value ≤ 0.157 .⁵ We repeated our calculations for the model on progression to a high risk situation with this P-value and found that higher p-value levels resulted in inclusion of more variables in the model. A few predictors were strongly influential and the remainder were relatively weak, as is often described in prediction models. Reducing the number of variables in the model by reducing the p-value level for inclusion of variables showed a similar ROC (0.69 vs 0.71) and better calibration (Figure 1a and b).

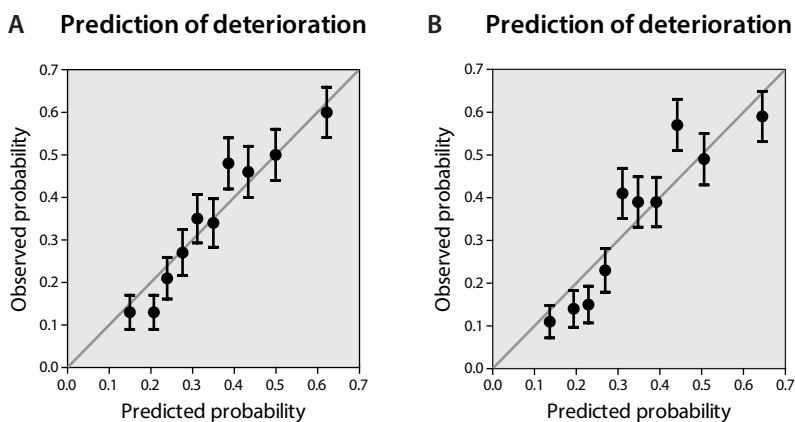


Figure 1a, P-value < 0.157 ; 1b, P-value < 0.40

Over the time period of this research clinical prediction models became more abundantly available. The knowledge on the methodology also developed. Reviews showed, however, that the quality of reports on the development and/or validation is poor. Recently, the TRIPOD statement (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) was developed, which describes a checklist for the reporting of studies on prediction models, to improve the transparency and completeness of reporting.^{6,7}

Before being able to implement these models in clinical practice external validation, *i.e.* testing the performance of the model in a new cohort, should be performed. The last step in developing a model consists of the evaluation of the impact on clinical outcome when implementing the clinical prediction model in clinical practice. If the risk estimate influences patient management, outcomes such as co-morbidity and quality of life can be compared to a situation in which no prediction model is used. This is something for future research. So at this moment we cannot advise a new model that should be used in clinical practice. However, it may well be that further research will prove the benefits of these models.

PART 2: FURTHER EVALUATION (CERVIX FAVORABILITY, BLOOD PRESSURE PATTERNS, CLINICAL IMPLICATIONS).

We showed that the characteristics of the cervix play a role in predicting delivery by caesarean section. For many years obstetricians believed that the success of labour induction is determined by the favorability of the cervix and that induction should be performed only when the cervix is ripe. In general, there is a reluctance to induce labour in women with an unfavorable cervix because of the fear of increasing caesarean delivery rate.^{5,6,8} In view of the observed beneficial effect of labour induction observed in the HYPITAT trial, the question is whether cervical ripeness should play a role in the decision to induce labour in these women. In other words, would women with GH or mild PE at term and an unfavorable cervix benefit less from labour induction compared with expectant management? Our analysis showed that the benefits of induction of labour could be found in women with an unfavorable cervix. We hypothesized that women with a favorable cervix are those more or less destined for spontaneous labour shortly; the potential for a preventive benefit from labour induction is smaller than in those with an unfavorable cervix. When evaluating the blood pressure pattern a higher caesarean section rate was found in the women who progressed to a higher blood pressure and/or severe disease, this was not influenced by induction of labour. So we concluded that development of severe hypertension is a risk factor for caesarean section, which explains the elevated caesarean section rates in the expectant monitoring group observed in the HYPITAT trial.

At the start of the HYPITAT trial in 2005, the optimal policy for women with pregnancies complicated by hypertensive disease at term was not clear, so there was a wide variation in management of women with GH or mild PE at term. After the HYPITAT trial we wondered whether the results had an impact on doctors'

behaviour and provoked an increased number of inductions of labour among women with hypertensive disease of pregnancy at term. We found that participation in the HYPITAT trial among others had immediate consequences for obstetric management and maternal health. The effect of the HYPITAT trial on management in women with GH was also evaluated by a group in the USA.⁹ Their objective was to examine the impact of the HYPITAT trial on management of gestational hypertension. Their cohort included 5077 women with GH who delivered between July 2008 and June 2011. The primary outcome was the rate of delivery intervention (either induction of labour or caesarean section) for GH. The rate of delivery intervention prior to the trial was 1.9%, compared to 4% after the trial ($P < 0.001$). They found no significant change in maternal and neonatal outcome. This difference with our analysis can possibly be explained by a small sample size since maternal complications are scarce at term. Second they only included women with GH. Women with mild PE may have a higher risk of maternal complications. One might imagine that after further research GH and PE will be managed differently, for instance induction in women with GH at 39 weeks and in women with PE at 37 weeks gestation.

FUTURE PERSPECTIVES

The HYPITAT trial concluded that induction of labour is associated with improved maternal outcome and should be advised for women with mild hypertensive disease beyond 37 weeks' gestation. In this thesis we made a start in developing models to individualize management and prevent unnecessary interventions, instead of rigorously inducing labour in all women with GH or mild PE at term.

Is there a future for these (or other) prediction models in obstetrics?

Personalized medicine is important but would be difficult without patient-specific risks. Current evidence suggests that multivariable models are the best way to estimate these risks. Prediction would not be necessary if there would only be one specific management for a condition in every stage of the disease. All patients would be diagnosed and the outcome (morbidity, complications, quality of life) would be the same. Since this is not likely to happen, *I think there is a future for prediction models and prognostic research in clinical medicine and also in obstetrics.*

SOME RECOMMENDATIONS FOR FUTURE RESEARCH

Several multivariate models have now been developed, but all of them need to be externally validated and studied for clinical impact, as do the majority of other prediction models developed in obstetrics. When is there 'enough' evidence? It is time to further evaluate the external validation and clinical impact instead of continuing to develop new models with the same, known variables. Or to evaluate new variables that may be associated with a certain outcome. There is not a gold standard to classify a model as "good". A model does not need to have excellent discrimination and calibration to be of clinical value; "all models are wrong, but some are useful".¹⁰ So it is

difficult to decide which model, or number of models to further evaluate. A model that is already validated is the full PIERS model, which also predicts a composite adverse maternal outcome in women with pre-eclampsia.¹¹ Although the model performed well in the development data as well as in a validation study, studies that assess the clinical impact are ongoing.¹² The HYPITAT data will be used to further evaluate the model before implementation.

The currently available prediction models estimate the probability of an adverse outcome associated with a given diagnosis, but further amplification would be necessary to increase their value in obstetric care. They now define a single risk, while multiple, simultaneous, risks may be at play and important to consider. Furthermore, the outcomes are often implicitly regarded as equivalent. Yet, they may have different degrees of severity and should therefore be assigned different weights. Finally, preferences of patients should be taken into account. Incorporating multiple outcomes and weights according to severity of outcomes is the next logical step. The development of such a decision tool requires comprehensive modelling of multiple clinically relevant outcomes, but will provide more insight in the consequences of treatment decisions in obstetric care. Once developed, such a tool could be implemented on a mobile platform for bedside use.

Besides the research described in this thesis, evaluation of induction versus expectant management in preterm pregnancies will also be interesting and important, since the risk of neonatal morbidity and mortality is higher and the period for women to progress to severe disease is longer. Recently the HYPITAT II trial was published, concluding that for women with non-severe hypertensive disorders at 34-37 weeks of gestation, immediate delivery might reduce the already small risk of adverse maternal outcomes.¹³ However, it significantly increases the risk of neonatal respiratory distress syndrome and therefore routine immediate delivery does not seem justified and a strategy of expectant monitoring until the clinical situation deteriorates can be considered. The combination of data from HYPITAT I and HYPITAT II will allow further evaluation of prediction models for the individual woman. In addition, we will further evaluate the impact and effects on maternal and neonatal health of nationwide, multicenter trials (HYPITAT, HYPITAT-II, PROMEXIL, and DIGITAT) that have been performed by the Dutch Consortium.

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