Personalizing obstetric care

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Valorisation

This chapter describes the (future) valorisation of the research described in this thesis. Valorisation can be defined as the process of value creation from knowledge, by making it applicable and available for economic or societal utilisation, and by translating it in the form of new business, products, services or processes\(^1\).

Relevance

In the Netherlands approximately 170,000 babies are born yearly\(^2\). Perinatal mortality, defined as stillbirths and deaths of infants within the first 28 days of life, is considered an important quality indicator of obstetric care\(^3,4\). By the turn of the last century, perinatal mortality, especially fetal mortality, was substantially higher in the Netherlands than in other European countries\(^5,6\). Five years later the situation had improved, but still the Netherlands, with its much-praised health care system, showed above-average perinatal mortality rates\(^7\). In 2008, a steering committee established by the Minister of Health Care published recommendations to optimize obstetric care, which resulted in a ZonMw research programme Pregnancy and Childbirth\(^8\). The four main priorities of the programme were aetiology of perinatal and maternal morbidity and mortality (1), health education and health promotion during the preconceptional period, pregnancy and postpartum period (2), risk selection and screening (3), and organization of obstetric care (4)\(^9\). In the meantime, the perinatal mortality rate (per 1000 births) substantially declined from 12.3 in 2000 to 7.3 in 2016 (Figure 1)\(^10\), and the position in the European ranking improved\(^11\).

In the Netherlands, 85% of the perinatal deaths go together with asphyxia, preterm birth (PTB), congenital anomalies, and small-for-gestational-age (SGA), also called BIG 4. A BIG 4 condition occurs in 16.3% of all pregnancies\(^12\). Pre-eclampsia (PE), a hypertensive pregnancy disorder, is associated with SGA and PTB, while gestational diabetes mellitus (GDM) increases the risk for infants born large-for-gestational-age (LGA)\(^13,14\). Infants born LGA are at increased risk for asphyxia and birth injuries\(^15\).

Early identification of women at increased risk of developing adverse outcomes during pregnancy is important considering the short- and, even more important, long-term health consequences for both mother and child. Early risk stratification provides opportunities for personalized medicine, the right intervention (treatment, prevention, diagnosis) for the right person at the right time and place from the right healthcare provider\(^16\). Tailored care may, next to reducing maternal and child morbidity and mortality, improve health-related quality of life, satisfaction with care, and reduce healthcare and societal costs. This thesis focused on improving personalised obstetric care in both early risk assessment (part I) and intervention strategies (part II).
Early prediction of adverse pregnancy outcomes

Obstetric care is based upon risk management, especially in the Netherlands, where the level of care is matched to the level of risk\textsuperscript{17}. Dutch primary care midwives work autonomously and monitor the pregnancy of women who are considered to be at low risk to develop pregnancy complications. Pregnant women at risk are assigned to an obstetrician in second or tertiary care. This unique system emphasizes the importance for early identification of women with a high probability to develop pregnancy complications\textsuperscript{18}. Around 85\% of pregnant women start antenatal care with a primary midwife and \textasciitilde{}55\% of these women are referred to secondary or tertiary care during pregnancy or labour\textsuperscript{5}. The obstetric indication list (VIL) is an official national guideline to judge the risk and need for referral\textsuperscript{19}. Although the guideline is evidence-based as much as possible, a drawback is that it is not an individual risk assessment tool, nor does it describe what the content of primary and secondary/tertiary care should be. Moreover, current risk management typically involves reaction to maternal and fetal problems when they already exist or are imminent, and contributes little to early detection or prevention.

Prognostic prediction models may be accurate tools to identify women at high risk for developing adverse pregnancy outcomes as multiple risk factors are combined in an algorithm, taking into account the risk dependent weight of each risk factor and possible interrelations\textsuperscript{20}. Several first trimester prediction models addressing important obstetric outcomes have been published\textsuperscript{21}. While the reported performance of numerous prediction models is promising, external validation studies are scarce and impact studies even more\textsuperscript{21}. External validation, which is the evaluation of the performance of the model in populations other than used for model development, is crucial before implementing a model in clinical practice\textsuperscript{22,23}.
In this thesis, the predictive performance of first trimester prognostic prediction models for the risk of PE, GDM, spontaneous PTB, and delivering an infant SGA or LGA among Dutch pregnant women was evaluated. Only models consisting exclusively of routinely collected maternal predictors were included as more ‘specialized’ tests (i.e. uterine artery Doppler or biomarkers) provide additional costs, might be inconvenient for pregnant women, and are not routinely performed or readily available in general antenatal settings\textsuperscript{24-26}. The latter is a particular important aspect when applying a prediction model in the unique Dutch obstetric setting. The studies in this thesis confirm the importance of an external validation study as nearly all models performed less well in our population. Moreover, as the currently published models have been developed in different countries among various types of populations and settings, evaluation of the predictive performance of all available prediction models in one independent Dutch cohort allowed for a fair comparison of the potential value in Dutch obstetric care\textsuperscript{27}. Furthermore, the clinical potential of the best performing models was evaluated as a prediction model can only lead to improved outcomes for both mother and child of they can guide healthcare professionals and individuals in their decision making regarding further management that are tailored to individual risk profiles. Besides prevention of adverse outcomes, the use of prediction models can also lead to a more efficient use of re-sources and refraining from unnecessary testing and interventions in low-risk women.

This thesis revealed that the best performing prediction models for PE and GDM are worth considering for application in Dutch clinical practice as follow-up management is available and models showed better performance compared to current risk strategies. Low-dose aspirin and calcium supplementation are efficacious and non-invasive interventions in the prevention of PE. In case of GDM, the prediction models can allow for targeted early screening by use of an oral glucose tolerance test.

**Prevention of adverse pregnancy outcomes**

A number of management strategies have shown to be effective in the prevention of adverse pregnancy outcomes. Calcium supplementation, one of the interventions that can be used, of at least 1000 mg of calcium per day during pregnancy lowers the risk of developing a hypertensive pregnancy disorder (PE and gestational hypertension), particularly among women with a low dietary calcium intake or at increased risk of developing a hypertensive pregnancy disorder\textsuperscript{28}. Despite its documented preventive effect, a minimal risk for side effects\textsuperscript{28,29}, and relative low costs (about €50 per pregnancy)\textsuperscript{30,31}, this approach is still not part of antenatal care in most countries. The World Health Organization recommends calcium supplementation as part of antenatal care in populations where calcium intake is low\textsuperscript{22}. However, also in populations with sufficient availability and affordability of calcium-rich foods, calcium supplementation among pregnant women is expected to have major public health implications.

This thesis indicated that almost two thirds of the pregnant women did not meet an intake of 1000 mg/day as recommended by the Dutch Health Council\textsuperscript{33}. The
contribution of calcium-containing supplements to total calcium intake was low. Although 64.8% of the women used supplements containing calcium, only 2% of the women used high-dose calcium supplements. Moreover, the calcium content of the most used supplements, prenatal vitamins, was insufficient for complementing the dietary calcium intake to reach the recommended adequate intake. The results of the decision analysis showed that advising calcium supplementation 1000 mg/day is a potential (cost-)effective intervention for implementation in Dutch antenatal care, with an expected reduction in the incidence of PE and net financial benefits up to 25% and €4,621,465, respectively. The economic benefits, i.e. health care and societal costs, may even be more favourable as long-term costs for both mother and child due to the burden of disease (i.e. cardiovascular disease or impaired neurodevelopment) were not considered. Although advising calcium supplementation to subgroups alone may be a more targeted approach, it might be more efficient to advise the use of calcium supplements to all pregnant women. In this way, women who are not part of defined subgroups also profit from the intervention and no individual dietary calcium intake or risk for developing PE has to be estimated. The results of the decision analysis were published, in addition to scientific journal, in the Dutch newspaper de Volkskrant (January 22, 2016) and subsequently by several other media sources (i.e. RTL news television, even across the border (VTM news Belgium). Recently, the Dutch Health Council recommends, also based on our decision analysis, that obstetric health caregivers should pay attention to an adequate calcium intake during pregnancy.

Translation of knowledge to personalized obstetric care
The studies in this thesis provide useful insights regarding prediction and prevention of adverse pregnancy outcomes, as described in more detail in the general discussion. Although further research towards improvement of prediction models, in particular among nulliparous women, and preventive measures is necessary, a next step towards optimization of Dutch obstetric care is to implement the findings in clinical care. While implementation is a task facing challenge, the medical literature has paid relatively low attention to this important step. Implementation efforts require that attention is paid to accessibility, affordability, acceptability, and adherence to the intervention strategies from a patient’s, care providers’, and organizational point of view. Changing caregivers’ and women’s behaviour is necessary to ultimately obtain the potential improvements of pregnancy outcomes and cost-effectiveness of care. A recent Dutch study exploring pregnant women’s perceptions, needs, and preferences regarding the use of prediction models for PE showed that women had a positive attitude towards screening. Although being confronted with an elevated risk could increase anxiety, self-monitoring together with better alertness and professional counselling were considered benefits of using a prediction model. In the end, an impact study is needed to determine whether implementation of the prediction models for GDM and PE and the recommendation to use calcium
supplements during pregnancy actually leads to the intended improvements. An impact study on the implementation of first trimester prediction models for PE and GDM combined with tailored care paths, and the recommendation to use calcium supplementation during pregnancy is currently performed in the south-eastern part of the Netherlands (Expect Study II). In April 2017, an early risk assessment tool (Expect Calculator, www.zwangerinlimburg.nl) was made available to primary as well as secondary/tertiary obstetric care. The tool provides, besides early risk estimation, personalized recommendations for antenatal care tailored to individual risks, which were developed by the Limburg Obstetric Consortium (midwives, obstetricians, and deputies of maternity care centres in Limburg). Moreover, the tool provides patient information brochures relevant to the patient’s risk profile. The Expect Study II will evaluate the adherence and compliance to the risk-dependent care by caregivers and pregnant women, respectively. Moreover, satisfaction and health care costs will be evaluated and compared to data of Expect Study I (before-after study).
References


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