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Modeling Renal Function During Pregnancy

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1 Abstract

The main goal of this research project is to build a computational model that illustrates the main processes in renal function during pregnancy. The analysis of how pregnancy affects all the factors that take place within the kidney will allow for a better understanding of how pathologies like proteinuria, hypertension, and glomerular endotheliosis develop. This model is a small part of a more complex model that showcases the complete pathophysiology of preeclampsia.

1 Introduction

The renal system is a central part of pregnancy, modeling its function complies with the purpose for further understanding how it affects and fluctuates throughout normal and preeclamptic pregnancies. There are a plethora of changes that occur to the kidneys, like increase in size, along with changes in elements like glomerular filtration rate (GFR) and renal plasma flow (RPF) that fluctuate as the gestation process advances. To arrive at the diagnosis of preeclampsia, the mother must have hypertension and/or proteinuria or end organ damage.

Up until this date, the only course of treatment to completely resolve symptoms is preterm birth, which may come with consequences and further complications if delivery is to happen before 37 weeks of gestation, or in the case that eclampsia develops. Preeclampsia is usually characterized by gestationally-related hypertension that happens after 20 weeks of gestation, and is thought to be caused by an abnormal placental blood vessel development during early pregnancy.

2 Literature Review / Annotated Bibliography

During preeclampsia, there is a decrease in GFR and renal plasma flow. Baylis, Davison, Moran, and Linheimer, et al. 2002 showcase data from normal, healthy pregnancies and compare it to data from preeclamptic pregnancies, both in late pregnancy and less than five months postpartum. This data helps to make the calculation of determinants in glomerular filtration. Evidence with glomerular filtration resolves in the sense that GFR determinants and modeled parameters were comparable across both postpartum groups.

Bia, Sosa, Torrado, Pereira and Zocalo et al. 2021 propose the hypothesis that the placental dysfunction could actually be related to a maladaptation of the mother's cardiovascular system for the pregnancy. They also talk about how our pathophysiological understanding has evolved to recognize impaired arterial function and structure during the early course of the pregnancy. It takes the fact that there are certain vascular features that are absent in preeclamptic pregnancies to analyze the role that arterial dysfunction plays.

Christensen, Edwards, Norden and Unwin et al. 2021 developed a mathematical model in order to better illustrate the contributions from glomerular infiltration and tubular uptake into the excretion of urinary protein. The model focused on protein reabsorption in the human proximal tubule (PT) with the basis on Michaelis-Menten kinetics and measurements referenced from Dent1 disease. It also aids to quantitatively predict the interaction between glomerular leak and hyperfiltration in the promotion of albuminuria. This model began from the difficulty to quantitatively interpret plasma protein presence in urine.

McElrath, Myatt, Rich-Edwards and Roberts et al. 2021 talk about the importance of defining different subtypes of preeclampsia, treating them individually instead of trying to comprise all of them into one syndrome. By recognizing them separately, it allows for better individual study of each condition, and proper prevention, evaluation, diagnosis, and care. This presentation reviews all subtypes defined from current information and makes suggestions for others.

The last article by Redman, Roberts and Staff et al. 2020 makes a presentation of the implications from preeclampsia. It presents how preeclampsia first begins to develop, with malplacentation and later decline in placental function which unravels in conditions like fetal hypoxia. A relevant occurrence during the second stages in both early and late preeclampsia include the syncytiotrophoblast stress. These are two pathways that ultimately end up sharing the same pathologic endpoint, syncytiotrophoblast stress. There are many pathways from which preeclampsia can arise, from genetics to environmental factors. This calls for a reassessment on how we can predict and prevent the arisal of preeclampsia.

3 Methodology

A. Initial Literature Research and Resource Learning

Before beginning the modeling process and the drafting for an initial diagram, I had to learn the basics of Vensim and renal functioning. For this, I began practicing Vensim through a graduate level course that I was granted access for by my mentor. This course included lots of resources and lab exercises to illustrate different problems in Vensim. I met with my mentor three to four times a week, where he would guide me through the basics of Vensim and where we would build simple models on things from real life like population (Figure 1) or modeling investments in a stock portfolio (Figure 2). After my meetings with my mentor, I would typically mess around with the models we were building together and try to implement different features to familiarize myself more with the structure in Vensim.

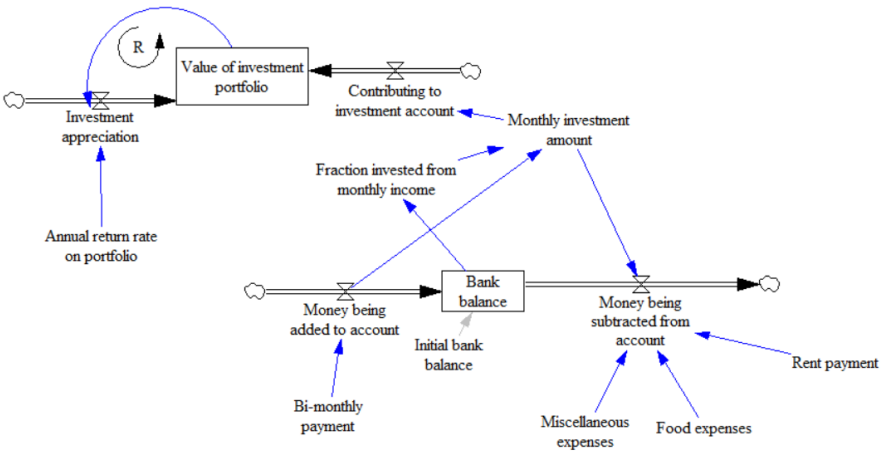

Figure 1: A model that represents the typical movements within a bank account. Includes elements like a bi-monthly payment going in, and the external factors that affect the money that gets subtracted from the account. A complex addition is the value of an investment portfolio. This tracks a fraction from the monthly income to contribute into the investment account, where it is later modeled over time.

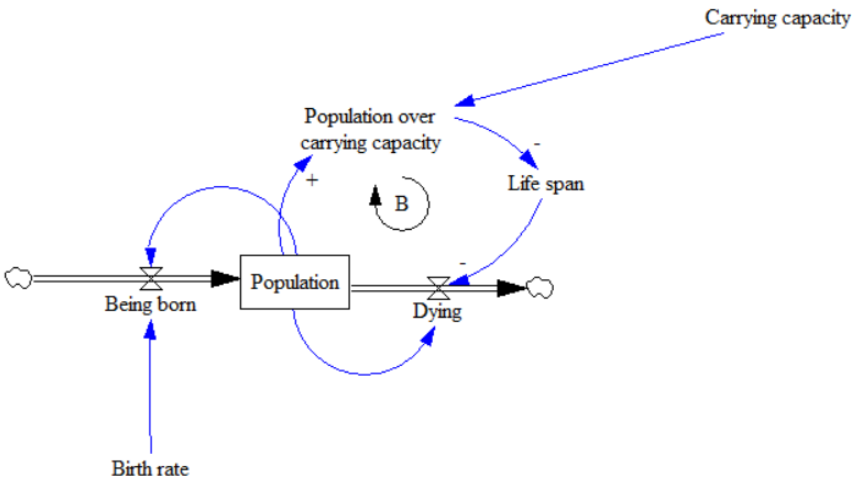

Figure 2: A computational model that illustrates population. It incorporates birth rate, death rate and life span, along with elements that make it more complex, like carrying capacity in a certain town.

With the help from the rest of the research team, I began reading through papers and analyzing the basic concepts in renal functioning, like glomerular filtration rate (GFR) and renal plasma flow. Later on, and as I developed more knowledge on the topic, I went back to dig deeper into more detail for these concepts. Since I had no prior knowledge in renal functioning, all of the terminology came foreign to me, which is why I eventually decided with my mentor to take a step back approach, and look at the big picture first before adding in details or more specific factors.

For the first two weeks, my main focus was learning as much as I could from all resources available, both in literature research and Vensim.

B. Incorporating Resources for Model (Vensim, Literature Review)

As I continued to develop my knowledge in both the renal physiology during pregnancy aspect and the functionality of Vensim, I also started some drafts for models based on some of the literature I was reading (Figure 3). I began diagraming in minute detail what I was reading in the literature. Later, much of the detail was removed, but starting with the details helped me to get a better feel on what a renal physiology model might look like in Vensim.

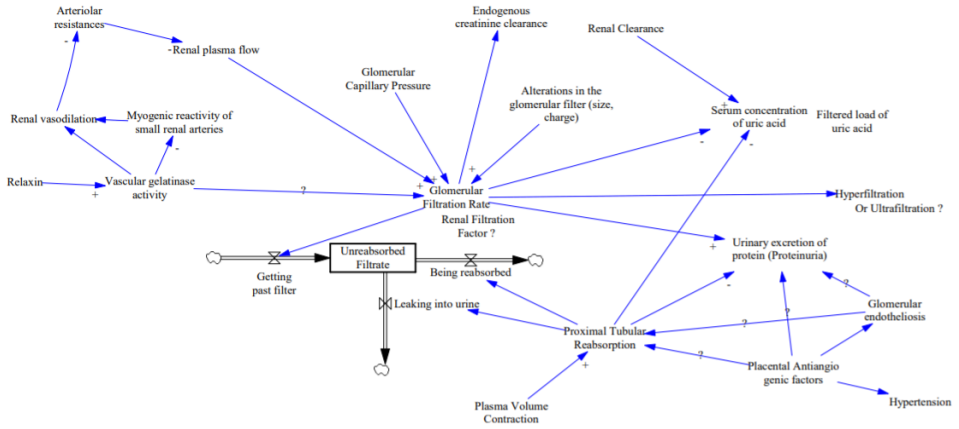

Figure 3: First version of the model. It is mainly based on the article Renal function during normal pregnancy and preeclampsia by Dr. Arundhathi Jeyabalan and Dr.Kirk P. Conrad, modified with the help from my mentor to illustrate our doubts on certain connections within the diagram.

C. Renal Function Model Diagram

Incorporating resources from the main research project and team (literature and the main model along other Vensim examples), I began to construct the first draft of the desired sub-model. The main issue was to decide what specific processes to start focusing on, as the renal system is quite complicated and we decided to start with a smaller scope. I based my initial draft on an article that compared renal plasma flow and glomerular filtration rate (GFR) between a normal, healthy pregnancy and one with preeclampsia. I soon realized after going through this process, that it would be better to take an even simpler approach to the concepts.

I decided to start over and create a new draft with a different focus as I completed more research on the concepts and developed a deeper understanding that allowed me to effectively model the system. Figure 3 shows the first original version of the model, along with an updated one that was modified with the help of my mentor. In this second modified version (Figure 4), there was some rearrangement of the variables to facilitate developing the equations. With elements that interact with each other on the left, moving towards the right to the outcomes.

Along with continuing my own research, there were still some specific details on concepts that were not as clear, so reaching out to experts on the matter was our next step. We met virtually, where I showed my diagram and received feedback. They also answered my questions thoroughly, and offered to send resources to better improve my understanding of the kidney to make my model more accurate and simpler.

D. Incorporating Mathematical Equations into Vensim Model Diagram

With the help from my mentor I began incorporating equations onto the updated diagram that got modified after hearing from the experts (Figure 3). As expected, there was a need for more through research on every individual concept placed into the updated model. Another essential part was to look for standard units of each of the elements, and the standard values for a non-pregnant woman vs a pregnant woman. All of these data would be able to get incorporated into the equations and therefore detect when pathophysiological phenomena typical in preeclampsia would develop, such as hypertension and albuminuria.

4 Results

Figure 4 illustrates the final version of the model. It has cleaner connections between all elements, and has parameters implemented to represent the non-pregnant values. This allowed for a better comparison for when pregnancy was present or not, and eventually changed as pathologies developed.

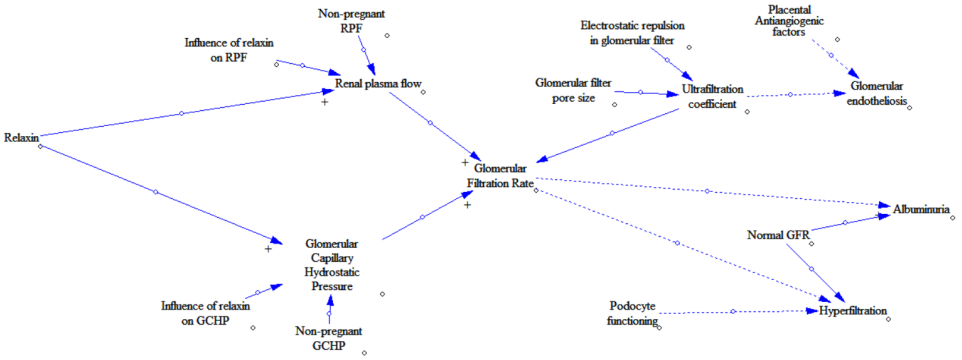

Figure 4: Final version of the computational model with the added equations.

The following is the set of equations used in Vensim to make the model fully computational. The majority of them focus on modeling the process rather than including the actual numbers present biologically.

(01) Albuminuria = IF THEN ELSE(Glomerular Filtration Rate > 2 * Normal GFR , 1 , 0) - Units: mg/d

(02) Electrostatic repulsion in glomerular filter = 1 - Units: nm/(sec*sec)

(03) FINAL TIME = 1 - Units: Month at The final time for the simulation.

(04) Glomerular Capillary Hydrostatic Pressure = "Non-pregnant GCHP"*(1+Influence of relaxin on GCHP*Relaxin) - Units: mmHg - Depends on levels for increase, and therefore affect GFR.

(05) Glomerular endotheliosis = Placental Antiangiogenic factors*Ultrafiltration coefficient - Units: Dmnl

(06) Glomerular filter pore size = 25 - Units: nm

(07) Glomerular Filtration Rate = Ultrafiltration coefficient * Glomerular Capillary Hydrostatic Pressure * Renal plasma flow - Units: ml/min

(08) Hyperfiltration = IF THEN ELSE(Glomerular Filtration Rate > 2 * Normal GFR , 1 , 0) + IF THEN ELSE(Podocyte functioning < 0.5, 1 , 0) - where 0 means false, 1 means GFR or podocyte is pathological, and 2 means both are pathological.

(09) Influence of relaxin on GCHP = 0.5 - Units: Dmnl

(10) Influence of relaxin on RPF = 1- Units: Dmnl

(11) INITIAL TIME = 0 - Units: Month at the initial time for the simulation.

(12) "Non-pregnant GCHP"= 4 - Units: mmHg

(13) "Non-pregnant RPF"= 7 - Units: ml/min

(14) Normal GFR = 1 - Units: mg/d

(15) Placental Antiangiogenic factors = 1 - Units: mmHg

(16) Podocyte functioning = 0.75 - where 1 means normal and less than 0.5 is serious dysfunction.

(17) Relaxin = 0.4 + STEP(0.2, 5) - Units: Dmnl - With 0.4 as the standard for late gestation.

(18) Renal plasma flow = "Non-pregnant RPF"*(1+Influence of relaxin on RPF*Relaxin) - Units: ml/min As the levels fluctuate, so would the amount of blood flowing through.

(19) SAVE PER = TIME STEP - Units: Month [0,?] - The frequency with which output is stored.

(20) TIME STEP = 1- Units: Month [0,?] - The time step for the simulation.

(21) Ultrafiltration coefficient = 0.02 + 0 * Electrostatic repulsion in glomerular filter * Glomerular filter pore size - Units: 1/mmHg

5 Conclusion

This model will help the main research team to incorporate greater detail into the more complete PE model. It is possible to represent the main processes taking place in the kidney during pregnancy, and the comparison between non-pregnant and pregnant aids in the illustration of how values may differ during normal and pathological (preeclamptic) pregnancies.

This research experience also provided me with the wonderful opportunity to work side by side with a research team, while also receiving mentorship on my own project. I developed knowledge in software like Vensim, along with growing my skills in reading scientific literature to identify useful data and information for my project. This internship has been a starting point for my career as a researcher.

6 Acknowledgements

This research project has been developed under the support of Dr. Wayne Wakeland, who aided in the creation of both the diagram and the incorporation of the equations. The models provided in this article were created to help a bigger research team incorporate detail into a more complex model. Members of this team included Dr. Arie Baratt, Mikhail Mints, Dr. Leslie Myatt, Dr. James Roberts, and Dr. Susan Bagby. This project happened through an NSF REU Summer Internship in 2021. The REU Site is supported by the National Science Foundation under grant no 1758006. Others involved in supervising and providing support were Dr. Christof Teuscher, Dr. Philippe Proctor, and the program coordinator, Adrian Jimenez.

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