A multiscale model for the feto-placental circulation in monochorionic twin pregnancies

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Abstract

We developed a mathematical model of monochorionic twin pregnancies to simulate both the normal gestation and the Twin-Twin Transfusion Syndrome (TTTS), a disease in which the interplacental anastomose create a flow imbalance, causing one of the twin to receive too much blood and liquids, becoming hypertensive and polyhydramnios (the Recipient) and the other to become hypotensive and oligohydramnios (the Donor). This syndrome, if untreated, leads almost certainly to death one or both twins.

We propose a compartment model to simulate the flows between the placenta and the fetuses and the accumulation of the amniotic fluid in the sacs.The aim of our work is to provide a simple but realistic model of the twins-mother system and to stress it by simulating the pathological cases and the related treatments, i.e. aminioreduction (elimination of the excess liquid in the recipient sac), laser therapy (removal of all the anastomoses) and other possible innovative therapies impacting on pressure and flow parameters.

Keywords: obstetrics, pregnancy, TTTS, mathematical model

1 Introduction

The Twin-Twin Transfusion Syndrome (TTTS), also known as Feto-Fetal Transfusion Syndrome (FFTS) and Twin Oligohydramnios - Polyhydramnios Sequence (TOPS), is a complication of monochorionic (one single placenta) twins pregnancy and it is diagnosed prenatally by ultrasound imaging. It consists in an alteration of the fetal circulation that results in an unequal distribution of the amount of blood from the placenta to twins: one of the fetuses (the Recipient or the Polyhydramnios) receives a lot of liquids, the other (the Donor or the Oligohydramnios) has a deficiency of them. Contrary to what someone could think, the more disadvantaged twin is the Recipient, in fact he/she suffers from hypertension, polyuria, circulatory overload and heart failures, diseases which could lead quickly to death; the Donor will suffer from anemia, hypotension, growth restriction and renal failures but he/she could survive

longer than the other twin.

Although being quite common (one case every 45 monochorionic twin pregnancies, about 6000 per year only in the USA), very few human data are available for mathematical models; in literature we found data from mammals (especially sheep, then dogs and monkeys) and some measurements on human fetuses in single [8] or twin [6]-[7] pregnancies.

The mathematical models proposed up to now to simulate the course of this disease are based on the hemodynamic and on the Windkessel ones. Many interesting simulations were published by Umur and Van Gemert [3] using data about the amniotic fluid volume, the blood pressure and the urine production. Their models produce very accurate results, but they needs a lot of input parameter values and measurements and they can not be used to study changes in time scale of minutes but only of weeks. The Windkessel model describes the interaction between the stroke volume and the compliance of the aorta and large elastic arteries: the total body circulation or, in this case, the system mother-fetuses, could be modeled by series of simple Windkessel circuits [5]. This model simulates accurately the changes in pressure and flow of the fetus in a time scale of seconds, but it could be computationally heavy if used to study the whole pregnancy.

The aim of our work is to create a multiscale model that could grasp the changes on a small time scale (minutes-hours), but that also allow to simulate long periods of time (weeks-months). In the section 3 we show our compartments model, in which the two fetuses are modeled as two compartments interacting with two distinct sources (the placenta); a discussion about the parameters is provided. In the section 4 some preliminary results, implemented in MATLAB (MATLAB and Statistics Toolbox 7.0, The MathWorks, Inc., Natick, Massachusetts, United States.) are shown.

2   Clinical definitions

The TTTS is characterized by anastomoses, links between blood vessels or leaf veins. Anastomoses are of three types: Arterio-Venous (AV), Venous-Venous (VV) and Arterio-Arterial (AA). The first one causes a unidirectional inter-twin transfusion because a placental cotyledon receives its arterial blood from one twin but drains its venous blood to the other: when one of the twin has a higher arterial (or venous) pressure than the other, this type of anastomoses may cause the TTTS. The other two types (AA and VV) directly link the two arterial or venous circulations and they are not strictly related to the TTTS.

Unfortunately, there is no primary prevention for TTTS; it could be diagnosed in different stages of the pregnancy and it could have dramatic modifications during time, e.g. the reverse of the twins (the Donor becomes Recipient and vice versa). Without therapies, the mortality for at least one of the fetuses for this disease is very high (more than 90%), but actually there are many ways to control and cure this syndrome. In particular, two therapy are now available and long experienced: the laser therapy and the amnioreduction. The amnioreduction is a symptomatic therapy consisting in a remotion of amniotic fluid (about 1.5-3 liters) from the Recipient sac. It is made puncturing the sac with the needle of a syringe and checking the fetus with the scanner. This technique should be repeated during the pregnancy and it is only a palliative, in fact it reduces the amount of the liquid in the Recipient but it does not act on the causes of the syndrome.

The laser therapy is the interruption of the connections of the placental vessels (the anastomoses) using laser. It is best used for moderate to severe (stages III and IV) TTTS, or twin size differences (discordance) of 40% or more, because there are procedure-related risks. However, it has the best probability of success: 55% of the birth of the two fetuses and 97% of the birth

of at least one.

3   The compartmental model

The aim of our work is to create a model which could link the amniotic volume information (and consequently fetus size) with the cardiac output of the fetus. We chose a compartment model in which the parameters are time-dependent and could vary rapidly in case of a perturbation of the system, e.g. the change of flow (laser therapy) or pressure in the umbilical cord.

At this stage, the model uses lumped parameters and steady-state values can be estimated while the time scale of the fetal heart rate $(< 1s)$ is disregarded. We made some hypothesis: the first one is that the fetuses are fed by different part of the same placenta and in the healthy case there are no connections between them or there is a balance of the flow in the anastomoses. The second hypothesis is that, for simplicity, the two part of the placenta which serve the two twins are considered 'infinite' sources; this means that the flow from the mother is constant and it always could compensate the demand for blood of the fetus. As concern the input and output flows between the fetuses and the mother, we consider two distinct types: the venous flow, from the mother to the fetus, that depends on the difference of their pressures and to the resistance of the vases; the arterious flow, from the fetus to the mother, that depends on the pressure generated by the fetal heart.

To ease the notation, we introduce also the quantities Π_∞ as the total carrying capacity of the sources Π_1 and Π_2, V_∞ as the total carrying capacity of the two amniotic volumes V_1 and V_2, $k = \frac{\Pi_1}{\Pi_\infty}$ as the percentage of liquid given by the first source and $1 - k$ as the percentage of the second one, $h_1(t) = \frac{V_1(t)}{V_\infty}$ as the percentage of liquid of the amniotic sac of the first twin and $h_2(t)$ the percentage of liquid of the second twin. The carrying capacities are introduced both to properly size the system and to limit the maximum volumes of liquids in play. Obviously, in this first model the carrying capacity of the sources makes little sense, in fact they are assumed constants, but they will assume greater significance in future models in which sources will have more complex expressions.

The ODE system becomes:

$$\begin{cases} \dfrac{dV_1(t)}{dt} = Q_{v1}(t)k - Q_{a1}(t)h_1(t) \\ \dfrac{dV_2(t)}{dt} = Q_{v2}(t)(1-k) - Q_{a2}(t)h_2(t) \end{cases} \tag{1}$$

where $Q_{v.}$ are the venous flows and $Q_{a.}$ the arterious flows (in day^{-1}).

In this case the two twins are not linked and they will develop separately (no TTTS is implemented). As concern the flow parameters, the arterious one is simply defined by the arterial pressure and it could be estimated using data from literature. The venous flow is more complicated to calculate, in fact previous works (see [1] for details) showed that it is related to the pressure of the mother and the fetus and also to the resistance of the vessels between them; moreover, this resistance varies with the gestation time and depends on the section and the length o the vessel (we used mean values from the literature). R_F is the resistance which varies throughout pregnancy.

$$Q_{v.} = \frac{P_\Pi - P_F}{R_F} \tag{2}$$

where P_Π and P_F are the pressures of the placenta and the fetus respectively, R_F the resistance of the fetus.

To model the TTTS, we inserted a new parameter that we called Q_{12}, the unbalanced flow from the first fetus to the second. It is a (fixed) quantity that must be added (or subtracted) to the venous flows. The system (1) becomes:

$$\begin{cases} \dfrac{dV_1(t)}{dt} = (Q_{v1} + Q_{12})k - Q_{a1}h_1(t) \\ \dfrac{dV_2(t)}{dt} = (Q_{v2} - Q_{12})(1 - k) - Q_{a2}h_2(t) \end{cases} \tag{3}$$

Note that, as shown in (2), the changes of the parameters, without therapies, take place few times during the pregnancy (weeks time scale): in each period the parameters could be supposed as constants. Supposing $Q_{v.}$ and $Q_{a.}$ constants, the system could be studied analytically; the solutions are:

$$\begin{cases} V_1 = \dfrac{Q_{v1} + Q_{12}}{Q_{a1}} k V_\infty + (V_1(0) - \dfrac{Q_{v1} + Q_{12}}{Q_{a1}} k V_\infty) e^{-\frac{Q_{a1}}{V_\infty} t} \\ V_2 = \dfrac{Q_{v2} - Q_{12}}{Q_{a2}} V_\infty (1 - k) + (V_2(0) - \dfrac{Q_{v2} - Q_{12}}{Q_{a2}} (1 - k) V_\infty) e^{-\frac{Q_{a2}}{V_\infty} t} \end{cases} \tag{4}$$

The more complicated case, with flow and carrying capacity parameters time-dependent, is not so easy to manage and it is not the aim of this our first work to find its analytical solutions.

4   Simulations of the treatments

The model presented in the previous section reproduces satisfactory the healthy case comparing our results with data from literature [3]-[5]. As concern therapies, we simulated both laser and amnioreduction with constants parameters: the amnioreduction was simulated changing the initial conditions at the time of the treatment, the laser therapy posing to zero the Q_{12} term. In recent times some clinicians combine the two therapies to improve and accelerate the result of the laser therapy. All the simulations are provided in Fig. 1.

As shown in literature, the amnioreduction does not cure the syndrome: it temporarily reduces the volume of liquids in the Recipient sac but the Donor twin does not benefit from the treatment. The laser therapy, instead, help both twins which tend to the healthy situation. The combination of both therapies seems to give an added benefit to the Recipient twin, although in our simulation this benefit is not greatly appreciable. The simulation of the complete model

Figure 1: Simulation of the three possible therapies. 1) single amnioreduction: the liquid of the Recipient twin decrease but it regrows rapidly in few days. The Donor twin has no benefits from the therapy, 2) laser therapy: the Q_{12} term becomes null after the surgery and both twin tend to the normal situation; 3) laser therapy combined with an amnioreduction: the Recipient twin has an additional benefit to reach the healthy situation.

with time dependent parameters is in development; we are working also on simulations of new therapies. In particular we are interested in to study how the system could evolve in case of fetal pressure perturbations.

5   Conclusion

We proposed a new model to simulate the healthy and the pathological case of a monochorionic twin pregnancy. Using a compartment model, we tried to combine the positive aspects of

both model types we reported in section 1, minimizing the criticalities. Obviously it is only a preliminary work that we would like to expand and deepen in the next future.

A distributed model may be devised as further step to account for the actual time dependent of the flows on shorter scales. This will allow for a more defined simulation of the heart pump and, moreover, will be able to simulate the flow waveforms, which can be clinically validated by Doppler flowmetry monitoring.

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