SPECIAL CONTRIBUTION

REVIEW OF STUDIES IN HUMAN PREGNANCY OF UTERINE AND UMBILICAL BLOOD FLOWS

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Abstract
Uterine and umbilical blood flow measurements are reviewed in terms of studies carried out in uncomplicated human pregnancies. The review includes the perspective of how those estimates of flow fit with current knowledge of human fetal O_2 consumption and uterine O_2 and glucose consumption. From the consideration of both the O_2 data and the flow measurements, we conclude that the best estimates for mean umbilical blood flow at term range between 120 and 145 ml•min^{-1}•(kg fetus)$^{-1}$. The uterine flow estimate from physiologic data would equate to ~270 ml•min^{-1}•(kg fetus)$^{-1}$. This estimate, based upon estimates of uterine O_2 and glucose consumption, is much higher than some estimates made by imaging techniques. The reasons for this discrepancy are not yet established. However, given the enormous variability in uterine flow measurements made with imaging techniques, it is clear that more research into improvement in these non-invasive approaches is still required and all current estimates of uterine flow must be regarded as rather crude trials.

Key words: fetal O_2 consumption, normal human pregnancy, umbilical blood flow, uterine blood flow, uterine O_2 consumption

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INTRODUCTION

In most of the studies of blood flows in human pregnancies, there is a dearth of attempts to integrate the data in any meaningful way with what is reasonably well established in terms of fetal oxygenation. Certainly, attempts to establish blood flows across the uterus or across the umbilical circulation are to be commended since it is flow, not velocimetry, that is vitally important in understanding tissue oxygenation. In theory, moving from velocimetry measurements to flow measurements seems reasonably straightforward since, if one knew the average velocity across a vessel and its diameter, the calculation of flow is simple. Unfortunately, both measurements of velocimetry and diameter have their errors. To focus on this problem, we shall first address measurements of umbilical blood flow (UBF) which might appear more straightforward than uterine flow measurements since there is a single, relatively large vessel, the umbilical vein that carries all of the flow. Remember that our reference point in searching for internal consistency of the data will be fetal and/or uterine oxygen consumption.

UMBILICAL BLOOD FLOW IN RELATION TO FETAL OXYGEN CONSUMPTION AND FETAL OXYGENATION

Table I summarizes the results of UBF measurements in normal human pregnancy during the third trimester (1-6). Note that the lowest value is only 56% of the highest values. This difference among mean values indicates that at least some of the studies were biased by large systematic errors in the calculation of blood flow. An excellent study by *Pennati* et al. (7) showed that the coiling of the umbilical vein in the cord changes the velocity waveform and leads to a consistent underestimation of umbilical blood flow of about 16%. It is important to realize that accurate UBF measurements would be a valuable step toward defining the normal rate of human fetal oxygen consumption. This rate defines the rate of fetal energy metabolism and is among the most basic bits of information concerning the physiology of human intrauterine life (8).

Fetal O_2 consumption equals UBF times the O_2 content difference between umbilical venous and arterial blood (Fick principle). This principle has been used in our laboratory

Table I. Umbilical blood flow per kg fetal weight (ml•min^{-1}•kg^{-1}) in third trimester human pregnancies.

Reference	Publication year	Gestational age (weeks)	Umbilical blood flow
Degani et al. (1)	1995	38	112 ± 25
Barbera et al. (2)	1999	38	104 ± n.a.
Rigano et al. (3)	2001	29	121 ± 34
Boito et al. (4)	2002	~37	78 ± 12
Di Naro et al. (5)	2002	39.5	123 ± 25
Acharya et al. (6)	2005	39	69 (51-93)

for routine measurements of fetal O_2 consumption in sheep, in connection with studies of normal fetal metabolism. In 162 fetal sheep studied ~2 weeks before term, the fetal O_2 consumption was 354±45 μmol•min^{-1}•(kg fetus)$^{-1}$ (mean±SD). The small SD of this mean (±13%) established that fetal O_2 consumption is a stable and reproducible aspect of normal fetal metabolism. Extrapolation of this information to the human fetus must take into consideration the fact that human body temperature is about 1 °C less than in the sheep. This suggests that human fetal O_2 consumption may be about 10% less than in the sheep. This estimate agrees with the observation that fetal heart rate is also about 10% less in humans than in sheep, ~160 in the sheep and ~145 in human fetuses. Since human and ovine fetuses have comparable heart/body weight ratios, it is reasonable to assume that this difference in heart rate indicates a proportional difference in cardiac output. The cardiac output in near term fetal lambs has been measured and is about 500 ml•min^{-1}•kg^{-1} (8). In considering the relationship of UBF to fetal O_2 consumption and to fetal cardiac output, we shall assume, for the reasons given above, a normal human fetal cardiac output of 450 ml•min^{-1}•kg^{-1} and fetal O_2 consumption of 315 μmol•min^{-1}•kg^{-1}, both values being 10% lower than the measured values in sheep.

A reasonably well established aspect of human fetal physiology is the oxygenation of the umbilical vein. *Marconi* et al. found that at 37 weeks gestation the umbilical vein O_2 saturation was 81±3% and the oxygen partial pressure (P_{O_2}) was 35±1 torr (9, 10), the latter value in good agreement with data of the human fetal oxygen dissociation curve studied *in vitro* (11). Mean fetal blood hemoglobin content was 13.5 g•dl^{-1} and the umbilical venous O_2 content about 6.6 mM. This value of umbilical venous O_2 content is relatively high, comparable to that of maternal arterial blood. However, all fetal organs are perfused by blood of substantially lower O_2 content. The only exception being the left lobe of the fetal liver, which is perfused primarily by oxygenated umbilical blood.

The blood leaving the fetal ventricles is a mixture of oxygenated umbilical blood and deoxygenated blood from the venous return of the fetal systemic circulation. The fetal cardiac output must then be partitioned into the UBF and flow to the fetal organs. Obviously, this partitioning must be balanced. If most of the blood went to the UBF, there would be insufficient flow to oxygenate fetal tissues. Conversely, if most blood went to the fetal tissues, the umbilical blood flow would be insufficient to sustain fetal oxygen consumption. This issue of the partitioning of fetal cardiac output has generated a mathematical model of the fetal circulation that describes the relationship between the two variables, UBF and the rate of O_2 delivery (μmol•min^{-1}) to the fetal organs (8). By this analysis, for any given value of umbilical venous O_2 content, fetal cardiac output and fetal O_2 consumption, the O_2 delivery is described by a quadratic equation that defines the UBF at which O_2 delivery to the fetal organs is at its maximum.

Figure 1 presents this relationship for these two variables, UBF and O_2 delivery to the fetal organs. It presumes representative values for umbilical venous O_2 content (6.6 mM), fetal cardiac output (450 ml•min^{-1}•kg^{-1}), and fetal O_2 consumption (315 μmol•min^{-1}•kg^{-1}). The umbilical flow at which O_2 delivery to fetal organs is at its maximum is 145 ml•min^{-1}•kg^{-1}, representing 32% of cardiac output. In sheep, the calculation of a maximum O_2 delivery underestimates the actual UBF by ~15%. The main reason for this difference is that there is preferential streaming of oxygenated blood to the fetal upper body. The function of this mechanism is to increase the blood flow to the fetal lower body by reducing the cerebral and coronary blood flows. In the human fetus, the cerebral/body mass ratio is about 8 times greater than in the ovine fetus and may shift a greater fraction of fetal cardiac output to the fetal upper body. Hence, it is possible that the two highest flow values in Table I (123 and 121 ml•min^{-1}•kg^{-1}) define most accurately the normal mean value of near term UBF in humans. At these umbilical flow rates, the O_2 content and saturation of umbilical arterial blood would be ~4 mM and 50%, respectively, in good agreement with mean normal values found in sheep (3.9 mM and 50% saturation). To the contrary, the lowest flow rates in Table I (78 and 69 ml•min^{-1}•kg^{-1}) are not consistent with general knowledge about fetal O_2 consumption, cardiac output and fetal oxygenation. Those flow rates imply mean value of umbilical arterial O_2 content (2.6 mM and 2.0 mM) and saturation (25% and 21%) that are found only in hypoxic fetuses.

UTERINE BLOOD FLOW IN NORMAL PREGNANCIES

Accurate and reproducible measurements of uterine blood flow in normal pregnancies are inherently much more difficult to obtain than those of UBF. Firstly, there is no single vessel that carries the entire flow. *Rigano* et al. (12) showed that the uterine arterial flow on the side closest to the placenta was almost 2 times the flow in the opposite side (292 *vs* 144 ml•min^{-1}) in late gestation. Similar differences were present in midgestation. These authors attempted to estimate total uterine flow by measuring flow in both the left and right uterine arteries. Whether the sum of these flows reported by *Rigano* et al. is approximately equal to

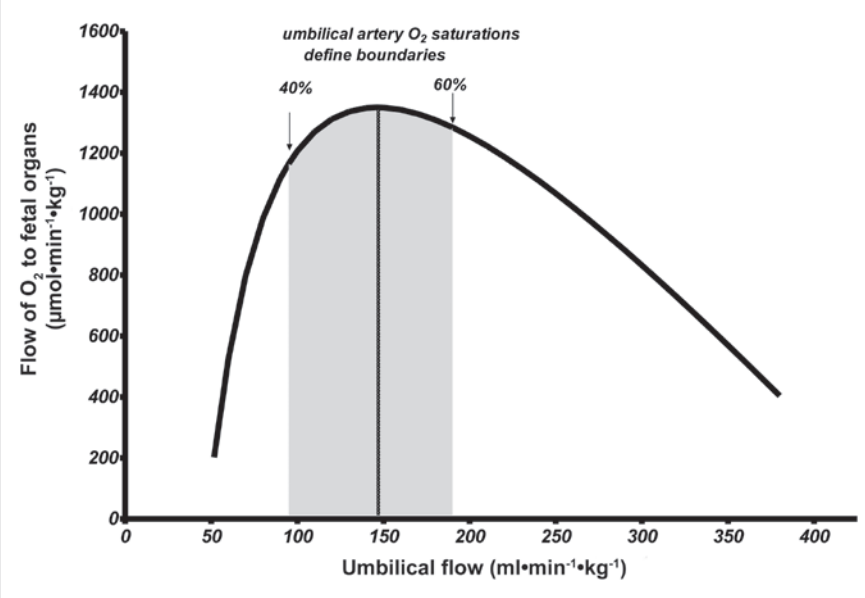

Fig. 1. Mathematical model (8) of the relationship of umbilical blood flow (f) to the flow of O_2 to the fetal organs (DO_2) for given values of umbilical O_2 content (6.6 mM), fetal cardiac output (450 ml•min^{-1}•kg^{-1}), and fetal O_2 consumption (315 µmol•min^{-1}•kg^{-1}). $6.6f^2$- ((6.6 x 450) + 315 – DO_2)f + 315 x 450 = 0
For any given value of fetal blood O_2 capacity, each point on the curve defines an umbilical arterial O_2 saturation value. The points corresponding to 40% and 60% saturations at normal 8.1 mM fetal O_2 capacity are shown.

Table II. Comparison of blood hemoglobin content (Hb), maternal arterial O_2 saturation (SA), and uterine venous O_2 saturation (SV) in term pregnant rabbits and sheep studied under normal physiologic conditions. These data can be used to calculate the uterine blood flow/uterine O_2 uptake ratio (F/VO_2).

Species	Reference	Hb (g•dl^{-1})	[O_2 capacity]^x (mM)	SA (%)	SV (%)	(F/V_{O_2})^{xx} (ml•µmol^{-1})
Rabbit	16	10.7	6.4	94	38	0.28
Sheep	17	11.4	6.8	95	78	0.87

^{x} [O_2 capacity] = Hb x 0.598
^{xx} (F/VO_2) =100/[O_2 capacity](SA-SV)

uterine flow remains an open question for two reasons. First, ultrasound measurements of uterine arterial flow involve complex methodological issues (13, 14) and the associated risk of systematic errors. Second, there is no information at this time about the contribution of the ovarian arteries to uterine flow. Also, there have been attempts to measure placental blood flow by means of the xenon washout method (15). Unfortunately, placental blood flow is only one of several factors that determine the placental washout curve of a gas that diffuses across the placenta (15). For this reason, the xenon washout method does not provide a reliable estimate of placental blood flow.

Physiologically, meaningful discussion of human uterine and placental blood flow must include a discussion of uterine venous O_2 saturation since there are large differences among mammals in its normal near term values. Table II presents a comparison of rabbit and sheep data (16, 17). The sheep data are for sheep homozygous for sheep hemoglobin A. This hemoglobin confers to the sheep blood an O_2 affinity similar to the human O_2 dissociation curve. The Table shows that, at comparable values of maternal arterial O_2 saturation, uterine venous O_2 saturation is about twice as high in the sheep than in rabbits. This information is relevant to a discussion of uterine blood flow because it can be used to calculate the uterine flow/O_2 uptake ratio. This ratio is about 3 times higher in sheep than in rabbits (Table II). The main reason for this difference in uterine O_2 extraction is that the maternal and fetal blood flows that perfuse the placenta form a venous equilibration exchanger in sheep, and a countercurrent exchanger in rabbits. In the ovine placenta, umbilical venous P_{O_2} tends to equilibrate with uterine venous P_{O_2}. However, equilibration cannot occur because the transplacental diffusion of O_2 is across a placenta that consumes O_2. Consequently, the oxygenation of fetal blood is subject to the boundary condition that umbilical venous P_{O_2} must be lower than uterine venous P_{O_2}. A high uterine blood flow/O_2 uptake ratio compensates for this by maintaining a high uterine venous P_{O_2}. By contrast, in a countercurrent placental system, umbilical venous P_{O_2} can be higher than uterine venous P_{O_2} because it tends to equilibrate with maternal arterial P_{O_2}. The countercurrent arrangement allows rabbits to maintain a normal level of fetal oxygenation at a much lower uterine flow/O_2 uptake ratio, one that would be fatal in sheep.

In an important study, the oxygenation of uterine venous blood has been studied in ten pregnant women that were

under epidural anesthesia and breathing atmospheric air at sea level (18). All fetuses were of normal weight at gestational age >37 weeks. The maternal arterial O_2 saturation was 97%. Uterine venous blood was sampled prior to a uterine incision for Cesarean section. The mean (±SD) uterine venous O_2 saturation and PO_2 were 79±8.4% and 45.9±6.5 torr, respectively. Uterine venous pH, PCO_2 and bicarbonate indicated a normal acid-base balance. Thus, according to this study, the normal arterial-venous O_2 saturation difference across the near term uterine circulation is ~18% (i.e., 97%-79%). Another inference from this study is that the normal uterine-umbilical PO_2 difference is ~10 mm Hg (i.e., 45 torr - 35 torr). These data are comparable to sheep data with a uterine arterial-venous O_2 saturation difference of 16.9%, and uterine-umbilical venous PO_2 difference of 14.2±1.2 torr (17). This evidence leads to the conclusion that, in the human placenta, the maternal and umbilical circulations form a venous equilibration system that requires a higher uterine flow/O_2 uptake ratio than the countercurrent exchanger or any other exchanger that would allow the umbilical venous PO_2 to be equal or higher than the uterine venous PO_2.

The prototype of a venous equilibrator is the concurrent exchanger. A model of this type is shown in the upper panel in Figure 2. In this model, maternal arterial blood (A) enters the exchanger with a much higher PO_2 than umbilical arterial blood (α). This PO_2 difference (i.e., 100 torr – 21 torr) drives the diffusion of O_2 into fetal blood. The transmembrane PO_2 difference tends to equilibrium (zero PO_2 difference) at the venous end of the exchanger. Hence, the term "venous equilibrator". Several conditions prevent full equilibration, in which case the uterine venous PO_2 remains higher than umbilical venous PO_2. Concurrent exchanger is not the only model of a venous equilibrator. A model which is more relevant to the human is shown in the lower panel of Figure 2. In this model, maternal arterial blood flows into a pool (intervillous space) that is vigorously stirred leading to a mixture with a single PO_2 value. The intervillous space approaches the condition of a "stirred pool" because the spiral arteries eject blood against the villous tree, which is not a rigid structure. It has villi which move in response to a pressure gradient perpendicular to the long axis of the villi. It is likely that the interaction between the maternal blood entering the intervillous space and the villous tree creates turbulent flow, i.e. a condition in which the velocity of red cells in most of the pool varies randomly in magnitude and direction.

Pregnant patients breathing atmospheric air at sea level, with normal lung function, have a virtually constant 97% arterial O_2 saturation. For these patients, one can construct a set of curves that relate the uterine blood flow/O_2 uptake ratio to uterine venous O_2 saturation, for any given value of blood hemoglobin concentration (see Equation 2 in Table II). Figure 3 presents 2 curves for hemoglobin values of 12 and 14 g•dl^{-1}, respectively. In order to estimate the magnitude of uterine blood flow from the graph, we need an estimate of uterine O_2 consumption. The rate of uterine O_2 utilization is greater than fetal O_2 consumption because the placenta and myometrial and endometrial tissues also consume O_2. In 16 near term sheep carrying a single fetus with a mean fetal body weight of 3035 grams, uterine O_2

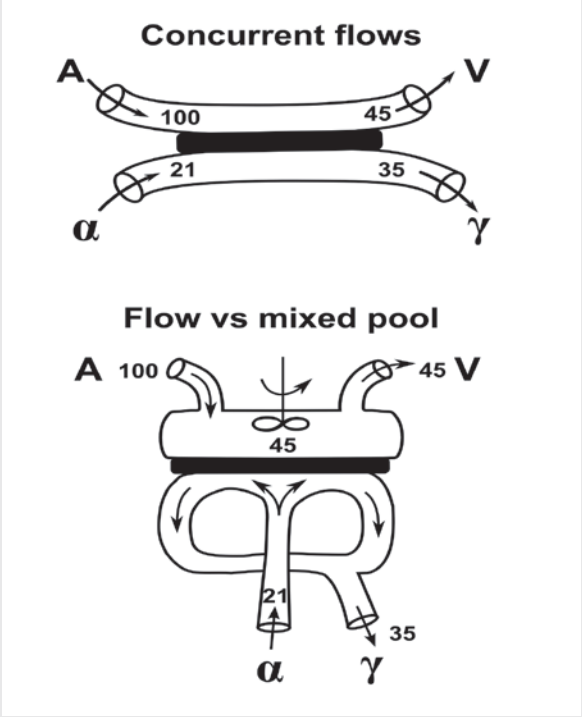

Fig. 2. Two models of transplacental venous equilibrator exchangers. In the concurrent flow model (upper panel), the placental barrier is interposed between maternal blood stream and fetal blood stream that run in the same direction. In the flow vs mixed pool model (lower panel), the placental barrier separates a stream of fetal blood from a stirred pool of maternal blood through which maternal blood flows. The numbers in the figure are PO_2 values (torr). A = maternal arterial, V = maternal uterine venous, α = umbilical arterial, ◘= umbilical venous.

consumption was 1630 μmol•min^{-1}. Of this total, only 1040 (64%) was fetal (17). Extrapolation to the human pregnant uterus suggests that for a 3-kg fetus having an O_2 consumption of 945 μmol•min^{-1} (i.e., 315 x 3), uterine O_2 uptake would be ~1480 μmol•min^{-1} (i.e., 945/0.64). At 80% uterine venous O_2 saturation, this O_2 uptake requires uterine blood flows equal to 1200 and 1040 ml•min^{-1}, at hemoglobin values of 12 and 14 g•dl^{-1}, respectively. The accuracy of this estimate is uncertain because there are substantial structural differences between the ovine and human placentas, differences which may be reflected in differences in O_2 consumption. However, for the sake of discussion, let us assume that the uteroplacental tissues of the near term human uterus consume O_2 at only ½ the rate of the comparable ovine tissues (300 vs 600 μmol•min^{-1}). This would reduce uterine O_2 consumption to 1245 μmol•min^{-1}, and the estimate of uterine blood flow required at each of the two maternal hemoglobin concentrations to 1019 and 872 ml•min^{-1}, respectively. These can be considered minimal estimates because the study of plasma glucose turnover in pregnant patients has led to the proposition that the human and ovine placentas consume glucose at ~ equal rates with the implication of a similarity for O_2 consumptions (19). Hence, it is clear that at 80% uterine venous O_2 saturation the magnitude of uterine blood flow is ~1 liter•min^{-1}. A decrease of uterine saturation to 70% would reduce uterine venous P_{O_2} by about 9 torr with

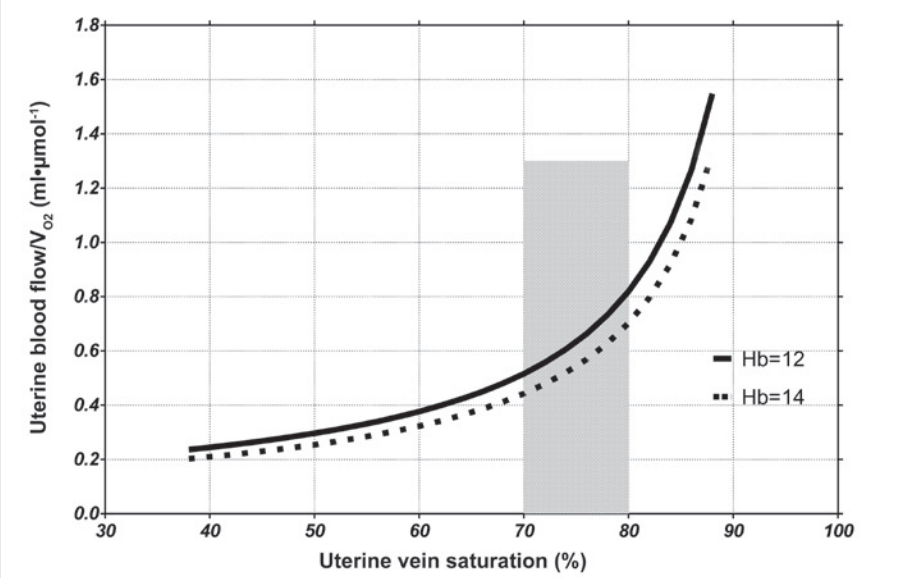

Fig. 3. Curves relating the arterial blood flow/O_2 uptake ratio to uterine venous O_2 saturation in pregnant women breathing room air at sea level, with blood hemoglobin of 12 and 14 g•dl^{-1}, respectively. Uterine venous O_2 saturation is in the 70%-80% range normally.

a similar decrease in umbilical venous P_{O_2}, which would result in a 20% reduction in umbilical venous O_2 content. This suggests that under normal physiologic conditions the uterine venous saturation ranges between 70% to 80%. If we then take as mean values 75% saturation and 13 g•dl^{-1} hemoglobin, we estimate that the normal fetal oxygenation of a 3-kg fetus requires a uterine blood flow of ~800 ml•min^{-1}, or ~270 ml•min^{-1}•kg^{-1}.

The question posed by our analysis is the following: How do we reconcile this analysis with the flow data already in the literature? Tables that summarize the results of uterine blood flow estimates can be found in two publications: Ref. 12 and Ref. 19. These tables make it apparent that there is no agreement as to the normal mean values of uterine blood flow at 36-38 weeks gestation. The highest reported mean value (20) is approximately twice the lowest and similar to the estimate we have made in this publication. This similarity could be coincidental, however. The presence of major unresolved technical issues is revealed, as well, by the large variability of measurements within a single investigation. Figure 2 in the publication of *Rigano* et al. (12) shows that, in the third trimester, the uterine blood flow measurements varied at random between 150 and 900 ml•min^{-1}. Contrast this result with the knowledge that, at any given gestational age, fetal O_2 consumption is a stable physiologic parameter and that, in near term ovine pregnancies studied under normal physiologic conditions, the standard deviation of uterine blood flow was ± 20% of the mean (17). Resting cardiac output in humans does not vary under normal conditions to the extent found for uterine flows in the literature, nor does blood flow to the brain or any other organ. Thus, there is no reason to assume it varies by this magnitude to the pregnant uterus.

Hence, there appears to be rather major technical difficulties still to be resolved. We have emphasized that the data for umbilical flow and fetal O_2 consumption is now reasonably well established and that gives us a firm foundation to proceed to examine future studies of uterine flow and uterine O_2 extraction. Hopefully, this review will provide some guidelines as to how that analysis can proceed.

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From the Vice-Editor

We are honored to receive a manuscript from two distinguished authors: Frederick C. Battaglia and Giacomo Meschia. The following is a brief introduction to these extremely experienced researchers for the younger readership. For the greater part of their scientific careers, both men have been associated with the University of Colorado School of Medicine, Denver, CO, USA, where they hold the positions of professor of pediatrics and obstetrics-gynecology and of physiology, respectively. Both have contributed to the literature of maternal-fetal medicine since the 1950s, with papers published in *Science*, *Nature*, *Journal of Clinical Investigation*, *American Journal of Physiology*, and *New England Journal of Medicine*, among others. Following publication of their seminal contribution to the study of fetal physiology, entitled '*An Introduction to Fetal Physiology*' (Academic Press, Orlando, FL, USA) in 1986, they were frequently referred to as the Fathers of Maternal-Fetal Medicine. Throughout their scientific careers, they have been editors, co-editors and reviewers for numerous scientific journals and experts for the National Institutes of Health, Bethesda, MD, and many healthcare-oriented foundations. Dr. Battaglia has served as President of the following societies and organizations: the Society for Pediatric Research, the American Pediatric Society, the World Association of Perinatal Medicine, the American Society of Pediatric Department Chairmen, the Perinatal Research Society, and the Western Society of Pediatric Research. He was conferred the title of Honorary D. Sc. from the University of Indiana in 1990. These two scientists have made enormous contributions to the modern understanding of carbohydrate and amino acid metabolism in the fetus and placenta, acid-base balance and blood gas exchange between the mother, placenta, and baby, many adaptative maternal changes to pregnancy, and the molecular basis for intrauterine growth restriction, to name a few of their research intensive investigations. The illustrative contribution published in our '*Developmental Period Medicine*' is a fascinating journey through their brilliant past achievements highlighting many of their findings crucial to our field.

Professor Maciej Jóźwik