Physiological Alterations during Pregnancy: Impact on Toxicokinetics

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During pregnancy there are physiological changes in several systems which can alter toxicokinetics in both the maternal and fetal compartment (Lewis, 1983; Mattison, 1986) (Table 1). These physiological alterations are required for successful pregnancy and lactation and result from resetting of maternal homeostatic mechanisms to deliver essential nutrients to the fetus and remove heat, carbon dioxide, and waste products from the fetus. The strategies selected by a given species for adaptation to pregnancy (Table 2) appear to depend upon the energy costs of pregnancy (Millar, 1976, 1980; Metcalf *et al.*, 1988). The energy costs of the physiological adaptations of pregnancy are not surprising given that the time from conception to weaning typically represents 3% of the total life span of an animal and during that time approximately 20% of the adult weight is developed (Peters, 1983).

GASTROINTESTINAL ALTERATIONS

In the human, intestinal motility is decreased and gastric emptying time increased (Hytten, 1980a). As a result of these changes in gut motility, xenobiotics will spend a longer time in both the stomach and the small intestine. If the xenobiotic is absorbed through the small intestine, increased residence time in the stomach may delay the time to peak concentration in the maternal compartment. In addition, the xenobiotic may be metabolized in the stomach so that increased residence time will decrease the amount of parent compound available for absorption. If the ingested xenobiotic passes through the stomach unal-

TABLE 1

PHYSIOLOGICAL CHANGES WHICH MAY ALTER TOXICOKINETICS DURING PREGNANCY

	Change
Absorption	
Gastric emptying time	Increased
Intestinal motility	Decreased
Pulmonary function	Increased
Cardiac output	Increased
Blood flow to skin	Increased
Distribution	
Plasma volume	Increased
Total body water	Increased
Plasma proteins	Decreased
Body fat	Increased
Metabolism	
Hepatic metabolism	±
Extrahepatic metabolism	±
Plasma proteins	Decreased
Excretion	
Renal blood flow	Increased
Glomerular filtration rate	Increased
Pulmonary function	Increased
Plasma proteins	Decreased

TABLE 2

FETAL GROWTH CHARACTERISTICS OF SELECTED MAMMALS

Characteristic	Human	Sheep	Guinea pig	Rat
Description of gestation				
Number of fetuses	1	1	3 (2–5)	11 (10–12)
Length of fetuses (mm)	280	147	67	21.5
Growth rate (g/kg/day)	15	45	70	350
Maternal pregravid wt (kg)	55	50	0.8	0.3
Birth weight (kg)	3.5	3.5	0.09	0.005
% maternal pregravid wt	0.6	7	34	18
Components of birth weight (%)				
Dry weight	30	19	25	14
Fat	16	2	12	1
Protein	12	12	12	12
Nonfat dry weight	14	16	14	—
Placental weight (g)	550	400	6.5	0.5
Energy cost of tissue accretion at term (kcal/fetus)				
Fat	5320 (560 g)	665 (70 g)	104 (11 g)	0.5 (0.05 g)
Protein	2350 (420 g)	2350 (420 g)	62 (11 g)	3.4 (0.6 g)
Total				
Per fetus	7670	3015	166	3.9
Per litter	7670	3015	498	42.9

Note. From Metcalf *et al* (1988).

tered, the longer time in the small intestine will increase the fraction of xenobiotic absorbed.

CARDIOVASCULAR ADAPTATIONS

Cardiovascular adaptations are thought to be important to establish adequate uterine blood flow (Moawad and Lindheimer, 1982), provide for fetal heat loss, and prepare the mammary gland for lactation (deSwiet, 1980a). In the human, cardiac output increases approximately 50% (1.5 liter/min) (deSwiet, 1980a). This increase occurs by the end of the first trimester and remains elevated over the remainder of pregnancy. Cardiac output is composed of two components: stroke volume (the amount of blood pumped with each beat) and heart rate. In the human the increase in cardiac output is accomplished by an increase in both stroke volume and heart rate (Table 3). Other animals, however, use different mechanisms to increase cardiac output in pregnancy. Increased cardiac outputs lead to an increase in blood flow to the uterus at term (Moawad and Lindheimer, 1982; Metcalf *et al.*, 1988). In women, uterine blood flow at the end of pregnancy is about 150 ml/kg/min.

TABLE 3

MATERNAL CARDIOVASCULAR ADAPTATION

	Cardiac output (%)	Heart rate	Stroke volume
Human	+50	+30%	+35%
Sheep	+30	+	+
Guinea pig	+20	−	+
Goat	+20	±	±
Rabbit	+20	±	±

TABLE 4

MATERNAL PULMONARY ADAPTATION

Function	Nonpregnant	Pregnant	Change (%)
Respiratory rate	15	16	±
Tidal volume (ml/min)	487	678	+39
Minute ventilation (ml)	7270	10,340	+42
Minute O_2 uptake	201	266	+32
Vital capacity (ml)	3260	3,310	+1

Note. Data from deSwiet (1980b).

This is comparable to uterine blood flow in the guinea pig, rabbit, and rhesus monkey (100 ml/kg/min), but considerably below those of sheep and goats (300 ml/kg/min).

In women, maternal blood volume increases about 50%, comparable to the increase observed in guinea pigs. Rabbits, sheep, and rats, however, appear to have smaller increases in blood volume during pregnancy. In all species studied, peripheral vascular resistance decreases during pregnancy. However, in humans after mid-gestation (20 weeks), peripheral vascular resistance begins to increase, and at term is at or above the peripheral vascular resistance at the start of pregnancy.

There are also substantial changes in blood flow to different regions of the body during pregnancy. Blood flow to the hand increases approximately sixfold (3 to 18 ml/min/100 ml tissue) during pregnancy (de Swiet, 1980a), and blood flow to the foot doubles (2.5 to 5 ml/min/100 ml tissue). Over this same period of gestation there are only small increases in blood flow to the forearm and leg.

TABLE 5

INCREMENT OF OXYGEN CONSUMPTION (ml/min)

	Weeks of gestation			
	10	20	30	40
Cardiac output	4.5	6.8	6.8	6.8
Respiration	0.8	1.5	2.3	3.0
Renal (Na)	7	7	7	7
Uterus	0.5	1.2	2.2	3.6
Placenta	0.0	0.5	2.2	3.7
Fetus	0.0	1.1	5.5	12.4
Breasts	0.1	0.6	1.2	1.4
Total increment	12.9	18.7	27.2	37.9

Note. Modified from Hytten and Chamberlain (1980).

RENAL ADAPTATIONS

In the human and the rat, renal blood flow increases during pregnancy. In rabbits, guinea pigs, and sheep, however, renal blood flow appears to remain unchanged during pregnancy (Davison, 1980; Metcalf *et al.*, 1988). One result of the increased renal blood flow during pregnancy in the human is an increase in renal size and energy utilization. The increase in renal size and energy utilization is a direct consequence of the increased renal blood flow. The increase in renal blood flow increases the glomerular filtration rate which removes increasing amounts of sodium. As sodium is the major extracellular solute it must be reabsorbed. In addition to the increase in reabsorption, the 6 to 8 liter increase in total body water requires an increase in sodium reabsorption. These alterations in renal blood flow and glomerular filtration rate may alter maternal renal xenobiotic elimination (Lewis, 1983; Mattison, 1986).

RESPIRATORY ADAPTATION

Pulmonary function also changes significantly during pregnancy (Table 4). Although

the respiratory rate is unchanged (deSwiet, 1980b), the tidal volume is increased. An increase in minute ventilation during pregnancy has also been observed in goats, sheep, cows, guinea pigs, and rats (Metcalf *et al.*, 1988). As a result of the increase in tidal volume there is an increase in the pulmonary distribution of gases, increased alveolar mixing, and a decrease in the time to reach alveolar steady state. Gas transfer, however, appears to be decreased due to interstitial changes in the lungs during pregnancy. For example, the pulmonary diffusing capacity of carbon monoxide is decreased from 26.5 to 22.5 ml/min/mm Hg.

The increased minute oxygen uptake is reflected in decreased arteriovenous differences in pO_2 during pregnancy and in increased oxygen consumption of approximately 40 ml/min (Hytten and Chamberlain, 1980). The components of the increased oxygen consumption early in pregnancy are predominantly cardiac output and renal sodium reabsorption. At term, however, the fetus, placenta, and uterus account for a substantial portion of the increase in oxygen consumption (Table 5).

SUMMARY

The physiological changes that occur in the alimentary, cardiovascular, pulmonary, and renal organ systems during pregnancy are designed to increase availability of nutrients to and remove wastes from the fetus. Although this is a general requirement, not all animals use the same strategies to meet these goals. These physiological adaptations will impact on toxicokinetics and may alter toxicodynamics. Absorption, distribution, metabolism, transfer between maternal and fetal compartments, and elimination will change for many xenobiotics during pregnancy. The changes in body weight, total body water, plasma proteins, body fat, and cardiac output will alter the distribution of many xenobiotics (Hytten and Leitch, 1971; Hytten and Chamberlain, 1980; Mattison, 1986). As the toxicokinetic parameters change across species, it is important to understand their impact on chemicals associated with maternal, placental, and fetal toxicity for appropriate cross-species extrapolation.

REFERENCES

DAVISON, J. M. (1980). The urinary system. In *Clinical Physiology in Obstetrics* (F. E. Hytten and G. Chamberlain, Eds.), pp. 289–327. Blackwell, Oxford.

DESWIET, M. (1980a). The cardiovascular system. In *Clinical Physiology in Obstetrics* (F. E. Hytten and G. Chamberlain, Eds.), pp. 3–42. Blackwell, Oxford.

DESWIET, M. (1980b). The respiratory system. In *Clinical Physiology in Obstetrics* (F. E. Hytten and G. Chamberlain, Eds.), pp. 79–100. Blackwell, Oxford.

HYTTEN, F. E. (1980a). The alimentary system. In *Clinical Physiology in Obstetrics* (F. E. Hytten and G. Chamberlain, Eds.), pp. 147–162. Blackwell, Oxford.

HYTTEN, F. E. (1980b). Weight gain in pregnancy. In *Clinical Physiology in Obstetrics* (F. E. Hytten and G. Chamberlain, Eds.), pp. 193–233. Blackwell, Oxford.

HYTTEN, F. E., AND CHAMBERLAIN, G. (1980). *Clinical Physiology in Obstetrics.* Blackwell, Oxford.

LEWIS, P. J. (1983). *Clinical Pharmacology in Obstetrics.* Wright PSG, Boston.

MATTISON, D. R. (1986). Physiological variations in pharmacokinetics during pregnancy. In *Drug and Chemical Action in Pregnancy* (S. Fabro, A. R. Scialli Eds.), pp. 37–102. Dekker, New York.

METCALF, J., STOCK, M. K., AND BARRON, D. H. (1988). Maternal Physiology during Gestation. In *The Physiology of Reproduction* (E. Knobil and J. Neill, Eds.), pp. 2145–2176. Raven Press, New York.

MILLAR, J. S. (1976). Adaptive features of mammalian reproduction. *Evolution* **31**, 370–386.

MILLAR, J. S. (1980). Pre-partum reproductive characteristics of eutherian mammals. *Evolution* **35**(6), 1149–1163.

MOAWAD, A. H., AND LINDHEIMER, M. D. (1982). *Uterine and Placental Blood Flow.* Masson, New York.

PETERS, R. H. (1983). *Cambridge Studies in Ecology: The Ecological Implications of Body Size.* Cambridge Univ. Press, Cambridge.