UMS PUBLICATION NUMBER 36(EDP) 1-31-80

THE NINETEENTH UNDERSEA MEDICAL SOCIETY WORKSHOP

# EFFECTS OF DIVING ON PREGNANCY

BETHESDA, MARYLAND

NOVEMBER 2-3, 1978

CHAIRMAN: WILLIAM P. FIFE

EDITOR: MARTHE B. KENT

UNDERSEA MEDICAL SOCIETY, INC.
9650 ROCKVILLE PIKE
BETHESDA, MARYLAND 20014

UMS Publication No. 36(EDP) 1-31-80

# EFFECTS OF DIVING ON PREGNANCY

Report of a Workshop

held on

November 2-3, 1978

in

Bethesda, Maryland

William P. Fife, Chairman

Marthe B. Kent, Editor

1980

Undersea Medical Society, Inc.
9650 Rockville Pike
Bethesda, Maryland 20014

This workshop was supported by the National Sea Grant Program of the National Oceanic and Atmospheric Administration, under Contract 04-8-M01-174.

*Reproduction in whole or in part is permitted for any purpose of the U. S. Government.*

*The opinions, conclusions, and recommendations in this report are not to be construed as official or necessarily reflecting the views of NOAA or the Undersea Medical Society, Inc.*

## Workshop Participants


Margie E. Bolton, R.N., M.S.N.
3311 N.W. 30th Avenue
Gainesville, Florida 32605

Alfred A. Bove, M.D., Ph.D.
Temple University Health Sciences Center
Philadelphia, Pennsylvania 19104

Charlotte Catz, M.D.
Head, Pregnancy and Perinatology
Child Health and Human Development
Bethesda, Maryland 20205

R.C. Cefalo, M.D.
Department of Obstetrics and Gynecology
University of North Carolina Medical School
Chapel Hill, North Carolina 27574

William P. Fife, Ph.D., Chairman
Chief, Hyperbaric Laboratory
Texas A & M University
College Station, Texas 77843

CDR K. M. Greene, MC,USN
Naval Medical Research Institute
National Naval Medical Center
Bethesda, Maryland 20014

John M. Hallenbeck, MC,USN
Naval Medical Research Institute
National Naval Medical Center
Bethesda, Maryland 20014

Michael A. Heeb, Ph.D.
National Sea Grant Program
Washington, D.C. 20235

Rev. Edward Lanphier, M.D.
Department of Preventive Medicine
University of Wisconsin
Madison, Wisconsin 53706

George Magaletta, M.D.
Southeast Missouri Hospital
Cape Girardeau, Missouri 63201

Martin J. Nemiroff, M.D.
Department of Internal Medicine
University of Michigan Medical School
Ann Arbor, Michigan 48109

John H. G. Rankin, M.D.
Madison General Hospital
Madison, Wisconsin 53715

Ms. Nancy Riegle
NOAA OE-3
6010 Executive Blvd.
Rockville, Maryland 20852

LT COL Paul J. Sheffield, B.Sc.,USAF
Brooks Air Force Base
San Antonio, Texas 78235

C. W. Shilling, M.D.
Executive Secretary
Undersea Medical Society
Bethesda, Maryland 20014

Arnold Simon, M.D.
Institute for Environmental Medicine
University of Pennsylvania Medical Center
Philadelphia, Pennsylvania 19174

Ms. KC Smith
Texas A & M University
Office of Sea Grant Programs
College Station, Texas 77843

Hakan Sundell, M.D.
Department of Pediatrics
Vanderbilt University Medical Center
Nashville, Tennessee 37203

J. Robert Willson, M.D.
University Hospital
Ann Arbor, Michigan 48109

Naida Yolen, Ph.D.
National Sea Grant Program
6010 Executive Boulevard
Rockville, Maryland 20852

## Preface

This workshop created so much interest that additional studies related to women and diving were continued, including both literature surveys and laboratory research. Results obtained in some of these subsequent studies have been incorporated into this final workshop report, although these additions were not considered by the workshop committee at the time of the original meeting.

C. W. Shilling
Undersea Medical Society

# Statement of Workshop Goals

This workshop had the following objectives:

1. To determine the maximum depth and time to which a pregnant woman can dive with assurance that her fetus will not be at greater risk than the mother herself.

2. To determine if female divers are at greater risk than male divers because of physiological changes that are specifically female or because of the effects of routine medication, such as oral contraceptives, diuretics, and analgesics.

3. To identify those areas in which our knowledge concerning women and diving is insufficient and which therefore require additional studies.

## CONTENTS



## APPENDIXES

# EFFECTS OF DIVING ON PREGNANCY

## EFFECTS OF DIVING ON PREGNANCY

The first known work on the effects of diving during pregnancy was published by Boycott, Damant, and Haldane in 1908 and consisted of a series of observations noting that pregnant ewes presented intravascular bubbles at autopsy after dives to 168 fsw (6.1 ATA) for periods ranging from 15 to 240 minutes. The authors concluded that a young fetus four inches or less in length had too active a circulation and too small a bulk to develop bubbles. Further, there were no bubbles even in an advanced fetus if the exposure lasted for 15 minutes or less. Unfortunately, this study was buried among Haldane's other work and did not receive attention until Bolton (1979) discovered it in her survey of the literature. Originally, this Haldane report went largely unnoticed, and it appears to have had no impact on the development of decompression tables. Because women were not engaged in diving at the time it was published, it did not stimulate further studies of this problem in the female diver.

In 1968, McIver exposed 28 anesthetized (with Nembutal) pregnant dogs to a stimulated depth of 165 fsw. Thirteen were exposed for a bottom time of 60 minutes, and 15 for 120 minutes. All of the 28 adult animals presented marked disseminating intravascular bubbles at autopsy. Two of the 94 fetuses of the first group and two of the 99 fetuses of the second group had bubbles in their coronary arteries, but no bubbles were seen in any other vessels. The amnionic fluid surrounding all 193 fetuses contained numerous large bubbles, but all fetuses survived the dives. In another series (McIver 1968), 23 newborn pups were exposed to air at a simulated depth of 165 fsw for 60 minutes, and eight showed marked bubbling throughout the vascular system.

Chen observed another instance of fetal resistance to decompression sickness in 1974. While using rats to study another problem, he noted that the fetuses of anesthetized pregnant rats did not show intravascular bubbles even though the mother developed fatal decompression sickness. Both of these recent studies (McIver 1968; Chen 1974) suggested that the fetus was more resistant to decompression sickness than the mother, which caused many workers to conclude that as long as a pregnant diver did not herself develop decompression sickness, her fetus was safe.

Here the matter rested until Fife et al. (1978) called attention to the fact that the placentas of both the dog and rat have a <u>countercurrent</u> arrangement between the maternal and fetal microcirculations, while the human placenta has a <u>concurrent</u> arrangement of the two microcirculatory systems. Since a concurrent arrangement is less efficient for exchange of substances between mother and fetus than a countercurrent system, data derived from dogs or rats should probably not be considered applicable to humans. This concern led to a search for an animal whose fetal/maternal microcirculatory dynamics more closely resembled that of humans. Van Cott (personal communication) suggested sheep as a model.

In 1978, Fife and his co-workers instrumented seven pregnant sheep by implanting Doppler ultrasonic transducers around one maternal jugular vein and one of the fetal umbilical arteries. Seventeen simulated air dives were made (Table 1). It can be seen from this table that even a dive considered safe for humans (100 fsw for 25 minutes) produced circulating air bubbles in the umbilical artery but did not produce circulating air bubbles in the maternal jugular vein. In fact, although circulating bubbles were detected in the fetus after dives to depths as shallow as 60 fsw, no bubbles were detected in the maternal jugular vein of any of the animals. Further, no clinical symptoms of decompression sickness were noted in any of the mothers after any of these dives, although it should be noted that in most cases as soon as bubbles were confirmed in the fetal circulation, the mother was recompressed immediately. It is possible that on some dives she might later have developed symptoms.

These observations suggested that the fetus of an animal having placental microcirculatory dynamics similar to those of humans might be at greater risk of decompression sickness than its mother. The Fife et al. study (1978) raised a number of questions:

1. Is the sheep a valid model from which to extrapolate to humans? Much research has been carried out on sheep in an effort to study fetal physiology, and in many instances these studies have improved our understanding of the physiology of the human fetus. It is clear, however, that the adult sheep is more resistant to decompression sickness than the adult human. If this also applies to their respective fetuses, it may be that dives that appear safe for a sheep fetus may be hazardous to a human fetus.

2. Does the sheep study by Fife and his co-workers (1978) show that the fetus is more sysceptible to decompression sickness than the mother? There has been some question about the validity of using the maternal jugular vein to detect circulating bubbles. Recent and ongoing unpublished studies of this problem being conducted in Fife's laboratory have revealed that the central venous system may contain bubbles when the jugular vein does not. However, these additional studies have confirmed that the dive profiles shown in Table 1 produced no clinical symptoms of decompression sickness in the mother even though circulating bubbles may have been present in the fetus.

3. Can the fetuses in the Fife et al. study (1978) be properly diagnosed as having decompression sickness? Decompression sickness is precisely defined in terms of pain, fatigue, and neurological manifestations; circulating bubbles are not included among these symptoms. Although it is widely recognized that there is no reliable correlation between circulating bubbles and clinical symptoms of decompression sickness, it is difficult to escape the fact that without recompression, the fetuses in this study would have died. Upon autopsy, all fetuses in which bubbles were heard showed widespread and massive intravascular

Table 1

Dive Profiles

| Dive No. | Depth, fsw | Time, min | Results Mother | Fetus |
|---|---|---|---|---|
| 1 | 160 | 20 | neg. | pos.** |
| 2 | 145 | 20 | neg. | pos. |
| 3 | 145 | 20 | neg. | pos. |
| 4* | 100 | 30 | neg. | pos. |
| 5 | 100 | 25 | neg. | pos. |
| 6 | 100 | 25 | neg. | pos. |
| 7 | 100 | 25 | neg. | pos. |
| 8 | 100 | 25 | neg. | pos. |
| 9 | 100 | 25 | neg. | pos. |
| 10 | 100 | 20 | neg. | thresh.† |
| 11 | 100 | 15 | neg. | thresh. |
| 12 | 100 | 10 | neg. | neg. |
| 13 | 80 | 40 | neg. | thresh. |
| 14 | 60 | 90 | neg. | thresh. |
| 15 | 60 | 70 | neg. | neg. |
| 16 | 60 | 60 | neg. | neg. |
| 17 | 40 | 200 | neg. | neg. |

*On this dive, the Navy Standard Air Decompression Table was followed; **pos. (positive) indicates presence of massive bubbles in circulation which probably would have been fatal; † thresh. (threshold) indicates the appearance of occasional acoustical events interpreted as probable circulating bubbles (however, treatment was not instituted) (Fife, Simmang, and Kitzman 1978).

bubbles in all organs. Further, most recent studies (unpublished observations) from Fife's Laboratory show that very short dives to depths deeper than 60 fsw almost invariably produce bubbles in the inferior vena cava of the adult sheep, even though these animals may not show clinical symptoms.

It has been agreed generally that since the fetus has a patent foramen ovale, any circulating venous bubbles should be viewed with alarm because they would invariably pass into the fetal arterial system. On the other hand, in the normal adult the lungs serve as a bubble filter that apparently protects against arterial gas emboli. These observations may necessitate an expanded definition of decompression sickness.

4. Is it possible that the bubbles observed in the fetuses are artifacts caused by surgical intervention? This question requires further study.

The workshop participants concluded that, though the Fife et al. (1978) preliminary study left many questions unanswered, its findings cannot be ignored because the consequences are too grave. These results call for great conservatism on the part of a physician advising a pregnant diver.

The most comprehensive study of pregnant women is being carried out by Bolton (1979); she conducted a survey by questionnaire of female divers throughout the world. A total of 208 certified divers who had been pregnant within the previous 5 years were included. Bolton divided her respondents into risk categories based on previous medical and obstetric history. Among 109 respondents who dived while pregnant, six (5.5%) had infants with birth defects; whereas, there were no abnormalities among 69 women who dived prior to but not during pregnancy ($p < .05$). Two infants with skeletan malformations, two with cardiac defects, and two with relatively minor malformations were reported. There was no definite relationship between depth or frequency of diving and malformation; however, there were three infants with birth defects among the 24 pregnancies of women who dived to depths greater than 100 fsw.

Since the diving Amas of Japan are the largest group of women known to dive regularly, they must be considered in any discussion of women and diving. It should be recognized, however, that all the Amas so far studied have been engaged in breath-hold diving. None of these divers used an underwater breathing device. Although it is clear that several repetitive breath-hold dives in a short period of time can cause decompression sickness, the Amas have not reported such symptoms. Because of the major differences between breath-hold diving and diving with an underwater breathing device, little can be gained by comparing these two types of divers. On the other hand, many Amas dive during pregnancy. Indeed, Mano (personal communication) reports that an Ama may occasionally bear her child on the beach. Epidemiological studies showed that 44.6% of diving Ama births are premature, compared to a 15.8% rate of prematurity in the non-diving population (Rahn 1965). It has been reported that some Amas now are using scuba; however, no data are available yet on the possible effects of the use of scuba on their pregnancies.

## Specific Diving-Related Problems

1. *Is a female diver who is not pregnant more susceptible to decompression sickness than a male diver?*

There is little information on which to base a comparison of male and female susceptibility to decompression sickness. It frequently is pointed out that all existing decompression tables were developed for young, healthy, male divers. Some European literature suggests that female divers are more susceptible to decompression sickness than their male counterparts, and there are observations by physicians, such as those by Nemiroff (unpublished observations), who believe that women are more susceptible to decompression sickness than men and that the disease is often more refractory in women than in men. This view is supported by an epidemiological study of female flight nurses exposed to altitude chambers (Bassett 1977). Although the numbers in this study were small, there was a 10-fold increase in decompression sickness in these females compared to their male counterparts. Further, these female cases of decompression sickness were more serious. They tended to have a more delayed onset and to be more severe, and were more difficult to manage than the disease in the males.

On the other hand, preliminary studies suggest that male Air Force cadets and para-scuba rescue trainees also had an approximately sixfold increase in altitude decompression sickness compared to the general U.S. Air Force population (unpublished data). Since the susceptibility to decompression sickness of these two special populations of young, healthy males approached that of the young, healthy female flight nurses, sex difference may not be the only major factor in bends susceptibility in these populations. It is recognized, of course, that there are some significant differences between decompression after diving and decompression to altitude.

The remarkably safe record of over 10,000 decompression-sickness-free decompression dives attained by the archaeologist Bass and his workers (personal communication)(approximately 25% of whom are females) may not provide much insight into female susceptibility to decompression sickness since this group routinely used the next deeper depth and the next longer bottom time to calculate decompression for these divers. These extra precautions would have placed all divers further into the safe zone and may have concealed any difference in susceptibility to decompression sickness.

Questions about the possible effects of oral contraceptives on susceptibility to decompression sickness have not been answered. Some physicians believe that since some oral contraceptives are reported to promote blood sludging, this effect could be additive to the tendency toward blood sludging seen in some cases of decompression sickness. No studies have addressed this question. A single preliminary study conducted at the Texas A&M Hyperbaric Laboratory (unpublished data) using Zorane on five pigs failed to show any increased susceptibility to decompression sickness in these animals after 30 days' use of this drug. This study must be considered inconclusive, but it would suggest that this oral contraceptive may not greatly change female susceptibility to decompression sickness.

Bangasser (1979) has recently completed a survey of decompression sickness among women scuba divers. She showed that the incidence of decompression sickness in women scuba instructors was about six times that of male instructors (0.043% for females and 0.007% for males).

Whether there are changes in decompression sickness susceptibility caused by the cyclical changes that occur in the non-pregnant normal female has not been studied rigorously. Bangasser (1979) found no effect in her study. Willson (personal communication) has pointed out that though males maintain a fairly stable physiological condition for long periods, female physiology changes on a monthly cycle. Major hormonal changes involve estrogen and progesterone levels which, in turn, alter the reproductive organs, electrolyte balance, and psychological status. The effects of these and other changes in the diving environment have not been assessed.

This workshop panel has no rigorous experimental evidence indicating that a female is more susceptible to decompression sickness than a male of the same approximate age and physical condition. In most instances, the safety factors designed into the standard sport diving tables make them safe even for individuals, male or female, who are slightly more susceptible to decompression sickness than members of the general population. Recognizing that females may have an increased susceptibility, some female divers arbitrarily calculate their decompressions by assuming their dive was to the next greater depth. The possibility that decompression sickness may tend to be more serious and more refractory to treatment in women than in men may be a greater cause for concern at present than the issue of female susceptibility.

*2. Is a pregnant female more or less susceptible to decompression sickness than a non-pregnant female?*

Decompression sickness susceptibility has not been studied definitively in the pregnant female. The workshop participants acknowledged that there are a number of circulatory, hormonal, metabolic, and body compositional changes in the pregnant female that could affect susceptibility. Theoretically, increased blood flow might be thought to increase the rate of gas transfer both to and from tissue beds. However, since it is probable that inert gas uptake during hyperbaric exposure is faster than gas elimination under the same apparent driving force during decompression, the increased circulation may not provide protection against decompression sickness. Results of many previous studies make clear that susceptibility to decompression sickness is directly related to body fat. Thus, although there is no experimental evidence that a pregnant woman is more susceptible to decompression sickness than her non-pregnant counterpart, workshop members believe this may be so. The standard decompression tables used by sport divers were not devised for a pregnant diver and may pose a risk to her if they are used close to the no-decompression limits. Panel members especially cautioned against performing saturation dives during pregnancy.

*3. What are the effects of diving on the maternal circulation during pregnancy?*

The direct effect of the fetus on maternal circulation must be considered. Fetal pressure on the iliacs and inferior vena cava may reduce blood flow from the lower extremities after a dive, which might interfere with the elimination of inert gas and thus alter the reliability of decompression predictions. Further, Bove (unpublished observations) noted that in pregnancy, supine hypotension, including syncope, may occur if the gravid uterus falls back against the inferior vena cava, reducing venous return. He suggested that assuming an equivalent position in the water could result in syncope after about the first trimester. This raises the question whether a tight-fitting wet suit could produce the same pressure.

Changes in uterine blood flow that may occur in the pregnant female while diving have not been studied in humans. There are, however, certain studies involving humans and animals that enable some consequences to be predicted. First, heavy exercise, stress, and increased levels of catecholamines are known to reduce uterine artery blood flow temporarily. Indeed, Rankin (unpublished observations) noted that the uterine placental vasculature is well supplied with alpha receptors. If excessive amounts of catecholamines are released, uterine blood flow falls to dangerous levels. On the other hand, many pregnant females jog or swim well into the third trimester without apparent complications. The workshop panel does not believe that the level of exercise involved in a quiet, relaxed, uneventful dive in itself imposes a detrimental cardiovascular stress on the pregnant female.

Second, uterine artery blood flow is decreased by high partial pressures of oxygen or certain drugs. Rankin (unpublished observations) noted that uterine artery blood flow in the sheep does not change significantly if the $PO_2$ is not elevated above about 700 mmHg. Assali, Kirschbaum, and Dilts (1968) showed in sheep that uterine artery blood flow was reduced an average of 10% when the dam was exposed to an inspired $PO_2$ of 3 ATA. These findings should be viewed in light of the fact that certain drugs such as aspirin also reduce uterine artery and ductus arteriosus blood flow. Whether or not these stimuli are additive is not known at this time. (The effects of elevated levels of inspired $PO_2$ on the fetus are discussed below.)

Third, the possibility must be considered that diving may create circulatory changes associated with hypertensive diseases or eclampsia. At present, there is no information to suggest that, within normal diving limits, an increase in hydrostatic pressure would have any effects other than the diving reflex on cardiovascular dynamics. It also should have no effects on the course of hypertensive disease. Any changes that occurred would probably be caused by emotional stress, exercise, or changes in $PO_2$ or $PCO_2$. Willson (unpublished observations) described several normal cardiovascular changes that occur in pregnancy. They include an approximately 30-35% increase in cardiac output by the end of the second trimester, unchanged or slightly falling systolic pressure, a 10-15 mmHg drop in diastolic pressure, and an increase in venous pressure in the lower extremities even in dorsal recumbency. Systemic vascular resistance decreases as the pregnancy progresses, probably because the uteroplacental circulation acts as a low resistance.

Temperature effects associated with diving do not appear to raise problems specific to the pregnant diver. There is no experimental evidence on the effect of extremely cold water on uterine artery blood flow. However, it is known that the pregnant Japanese diving Ama spends many hours each day in water that may be as cold as 10°C, and although her child tends to be small at birth, there is no evidence that the infant has suffered the effects of reduced uterine artery blood flow (Rahn 1965).

The effect of the diving reflex also must be considered, although this reflex is not as strong in humans and other land mammals as in marine mammals. It can however be demonstrated to some extent in all the land animals so far tested. This reflex consists of a reduced heart rate and a reduction in blood flow to all organs of the body except the lungs, heart, and brain, and is elicited by holding the breath and submerging the nose and mouth in water. The degree of response is inversely related to the temperature of the water. The diving reflex may reduce the heart rate in the diving Ama by as much as 50% (Rahn 1965). Although no measurements of uterine artery blood flow have been made in humans during breath-hold diving, it is reasonable to assume that uterine artery blood flow is reduced by the diving reflex. Scuba divers do not elicit this reflex to any significant degree because they do not hold their breaths. The uterine blood flow in pregnant human scuba divers would not therefore be expected to respond to the diving reflex to any significant degree.

Fourth, the effects of diving on various hematological components in the pregnant woman should be explored. Usually, diving causes no significant change in blood enzymes. In some caisson worker accidents, creatine phosphokinase levels have risen, but it has usually been possible to correlate this with a specific trauma. However, Nemiroff (unpublished observations) pointed out that this occurrence is no marker for decompression sickness. There usually is a rise in blood cholesterol levels during diving but no mechanism explaining this has been positively identified. Some workers (personal communication) believe an increase in cholesterol is a response to a non-specific stress.

It is well known that the number of blood platelets decreases after diving. In some if not all instances these probably are removed by platelet-lipid aggregation on venous bubbles that then lodge in the lungs. The effect of a reduction in circulating platelets on blood coagulation in the pregnant diver has not been studied. In unpublished experiments (Brown 1979), large numbers of bubbles were detected by Doppler detectors implanted on the inferior vena cava of sheep after dives to 60 fsw for a bottom time of only 2.5 minutes, followed by decompression to the surface at a rate of 60 feet per minute. These bubbles would be expected to remove a large number of platelets from the circulation. It is not yet known how shallow a particular dive must be to ensure that no circulating venous bubbles are produced. Further, it is not known if the depth and time of exposure necessary to develop these venous bubbles are species specific. It must be assumed that most humans using similar dive profiles would develop venous bubbles. This observation suggests that a physician concerned about the coagulation time of a pregnant patient should be cautious.

In general, the workshop panel concluded that while the mild exercise associated with diving would be beneficial to cardiovascular conditioning, it is not clear how strongly the uterine artery blood flow responds to emotional stresses, hypoxia, hyperoxia, hypercapnia, or to many drugs. The well-being of the healthy <u>pregnant woman</u> (without consideration of the fetus) would not seem to be compromised by non-strenuous diving to depths less than 4 ATA. In fact, the increased external pressure of water on the extremities and the tendency to be in a horizontal position might even reduce lower extremity pooling and improve venous return.

The principal concern of the workshop participants, as expressed by Nemiroff, was that if it became necessary to expose a pregnant patient to hyperbaric oxygen, either because of treatment on USN Treatment Table 5 or 6A or for therapy of a non-diving disease, the effects on either the mother or the fetus could not be foretold with certainty. Further, little is known about the effects of a hyperbaric environment on the efficacy of drugs. Pregnancy would add an additional unknown factor to the attending physician's dilemma. Physicians experienced in hyperbaric medicine recognize that the effects of some drugs and procedures cannot be predicted in the hyperbaric environment, and they do not welcome the additional problems raised by pregnancy. The workshop members are aware that Hart (personal communication) has used hyperbaric oxygen therapy on two pregnant women for non-diving related diseases. This author reported that both patients subsequently delivered normal children. The majority of the workshop participants believe that hyperbaric oxygen therapy should not be withheld from a pregnant patient if the need is clear and the disease or condition being treated falls into Category I or II of the Undersea Medical Society's report on hyperbaric oxygen therapy (Undersea Medical Society 1977). On the other hand, workshop members recommend that no pregnant woman voluntarily engage in any activity that might cause her to need hyperbaric oxygen therapy.

## Problems of Fetal Homeostasis

Diving's potentially adverse effects on the fetus may extend beyond susceptibility to decompression sickness. Since both compressed air diving and hyperbaric oxygen therapy raise the inspired $PO_2$ level, the following questions about the effects of exposing a pregnant female to high partial pressures of inspired oxygen have been raised.

*1. What effect does an increased maternal $PIO_2$ have on fetal arterial $PO_2$ and therefore on possible fetal oxygen poisoning?*

This question was studied by Assali and his associates (1968) in the pregnant sheep; these workers found that when the mother was exposed to an inspired $PIO_2$ of 2280 mmHg, her arterial $PO_2$ rose to 1200 mmHg, and fetal umbilical vein $PO_2$ rose from an average of 37 mmHg to an average of 335 mmHg. Thus, there was a significant rise in the amount of oxygen supplied to the fetus under these conditions. On the other hand, Rankin (unpublished observation) reported that the fetus will not be exposed to a high $PO_2$ if the mother does not breathe oxygen at a partial pressure above about 700 mmHg, equivalent to an air dive of about 100 fsw. These findings indicate that the fetus may not become hyperoxic during a normal air dive. However, a problem may arise if the mother is exposed to pure oxygen at 3 ATA, as is common during hyperbaric oxygen therapy. In one study in sheep, the average umbilical vein $PO_2$ was raised from an air breathing level of 31 mmHg to 458 mmHg during oxygen breathing at 3 ATA (Assali 1968). This remarkable elevation of fetal arterial $PO_2$ raises the possibility of oxygen toxicity. Fujikura (1964) has shown in rabbits that maternal exposure at these levels resulted in retrolental fibroplasia in the unborn fetuses.

Greene (1975) refers to work by Miller and his associates (1971) and others (Ferm 1964; Telford et al. 1969; Pizzarella and Shircliffe 1967) that suggests that hyperbaric oxygen may have teratogenic effects on the fetuses of some vulnerable species such as hamsters, rats, and chicks. Greene noted that since these higher levels of oxygen were studied in intact animals, it was not possible to determine the precise level of oxygen to which these fetuses were exposed. However, in the chick studies (Pizzarella and Shircliffe 1967), the eggs were exposed directly to 1 ATA of oxygen, which probably caused an approximately one-ATA direct exposure of the embryo to oxygen. Bolton (1979) noted that chicks also developed abnormalities when exposed for 8-9 hours to 4 ATA of compressed air. (Compressed air at 5 ATA approaches the same $PO_2$ as pure $O_2$ at 1 ATA.) Although it is possible that the umbilical vein $PO_2$, which is known to range between 204 and 698 mmHg, could be teratogenic, Assali's work (1968) reveals that even though the umbilical vein blood contained such a high $PO_2$, the fetal pulmonary artery blood contained a $PO_2$ of only 38 to 61 mmHg at the same time. This oxygen level probably more accurately reflects the $PO_2$ to which most of the developing tissues are exposed during hyperbaric oxygenation at 3 ATA.

In Fife's laboratory (unpublished observations), three pregnant ewes were exposed to as many as eight complete hyperbaric oxygen treatment tables (U.S. Navy Tables 5 and 6A) during the last trimester and were allowed to survive to delivery. To date, none of the lambs has developed retrolental fibroplasia or any other recognizable abnormality. As already mentioned, Hart (personal communication) treated two pregnant women with hyperbaric oxygen therapy, and, although the duration of treatment was not specified, both infants appeared normal at birth.

The workshop members did not feel satisfied about the lack of experimental data upon which to assess the potential damage to the unborn fetus from oxygen toxicity. The rabbit and rat studies (Ferm 1964; Telford et al. 1969; Fujikura 1964; Miller et al. 1971) previously mentioned did not expose the experimental subjects to oxygen levels and times similar to those used in human treatments. Further, fetal rabbits are known to be especially susceptible to retrolental fibroplasia. On the other hand, some of the teratogenic defects observed in the offspring in these two studies were severe and must be avoided in humans. The Fife sheep studies (1978; unpublished observations) and the two human cases (Hart, personal communication) just mentioned are not specifically relevant, since the fetuses in these research efforts were in the third trimester, beyond the period when teratogenesis might be expected. The panel concluded that fetal oxygen poisoning would not be anticipated on a compressed air scuba dive, but this question has not been thoroughly investigated.

*2. What is the effect of an elevated maternal inspired $PO_2$ on the fetal circulation?*

Studies by Assali et al. (1963, 1968) provide some examples of fetal blood flow changes that occur when the mother is exposed to an inspired $PO_2$ equal to 3 ATA. However, these were acute studies carried out on sheep, and they may not therefore reflect the response of a normal human fetus. Table 2 is a summary of some of these findings.

This table shows that hyperbaric oxygen at 3 ATA reduced ductus arteriosus flow to 16% of its control value, while pulmonary artery blood flow increased about 20%. Since cardiac output was essentially

Table 2

Fetal Blood Flow Changes Resulting From Maternal Exposure to Oxygen at 3 ATA

| | Mean Arterial Pressure, mmHg | Pulmonary Artery Flow, ml/kg/min | Ductus Flow, ml/kg/min |
|---|---|---|---|
| Control | 67 | 153 | 96 |
| HBO | 67 | 183 | 15 |
| Recovery | 65 | 176 | 107 |

Values are averages from 8 animals (Assali et al. 1968).

unchanged, there was a major increase in the work of the right heart. The perhaps adverse effects of this on a fetus are not known, but increasing cardiac load in a fetus already under stress would certainly be inadvisable.

There are no studies known that examine the effects on the fetus of having the mother exposed to a moderately increased inspired $PO_2$ level during a compressed air dive. An air dive to 100 fsw would result in an inspired $PO_2$ approximately equivalent to that caused by breathing pure $O_2$ at 0.84 ATA. In the absence of other information, it is probably wise to assume that the reduction in ductus arteriosus blood flow would be inversely related to the elevation of maternal $PO_2$. If this is indeed the case,a dive to 132 fsw on compressed air could cause a 19% drop in ductus flow and a comparable increase in pulmonary artery flow (based on Table 2 data). Even this reduction might constitute an insult to some fetal hearts; a 10% variation in these flows is probably within an acceptable range that is not dangerous to a normal fetus, but a 19% reduction or increase might be undesirable.

The studies by Assali and his co-workers (1968) also showed that exposing the mother to hyperbaric oxygen at 3 ATA caused a decrease in umbilical vein blood flow from 173 ml/kg per minute to 156 ml/kg per minute (Table 3), which represented only a 10% decrease in blood flow. The elevation of $PCO_2$ and the associated drop in pH should be well tolerated by a fetus for short periods. Carbon dioxide retention probably was caused by the reduction in umbilical vein blood flow and the fully saturated hemoglobin (Table 3).

Uterine artery blood flow does not change as much as ductus blood flow does in the presence of high $PIO_2$. Assali's work (1968) showed only a 17% drop in uterine artery blood flow in sheep when the mother was exposed to inspired oxygen at 3 ATA. It would seem, therefore, that an inspired oxygen level of 1.5 ATA would not reduce uterine artery flow by as much as 8-10%. Thus,if uterine artery flow was the only consideration, the mother should be able to dive to 203 fsw on air. However,

Table 3

Umbilical Vein Blood Flow and Gas Content

| | Umbilical Vein Blood Flow, ml/kg/min | Umbilical Vein Blood | | |
|---|---|---|---|---|
| | | $PO_2$, mmHg | $PCO_2$, mmHg | pH |
| Control | 173 | 26 | 30 | 7.38 |
| HBO | 156 | 319 | 41 | 7.28 |

Data derived from Assali et al. 1968.

if the ± 10% variaton in ductus flow discussed above is accepted as a a reasonable limit for the fetus to tolerate, the mother should not dive to depths deeper than about 53 fsw. This limit is of course arbitrary and cannot now be supported by experimental results. For example, Rankin (unpublished observations) noted that slight elevations in maternal arterial $PO_2$ may not be passed on to the fetus. For the sake of the fetus, however, panel members felt that pregnant women should be careful, at least until results of more definitive hyperbaric oxygen studies are available. The workshop members recommend, therefore, that any proposed hyperbaric treatment of a pregnant female be carefully considered to ensure that the need justifies the risk. Hyperbaric oxygen should be used without hesitation when the mother's life is threatened, and its use should be restricted to treatment of those diseases listed in Categories I and II of the Undersea Medical Society's workshop report on hyperbaric oxygen therapy (1977).

*3. What are the possible effects of hypoxia or asphyxia on the fetus?*

There are several ways in which a diver can suffer hypoxia or asphyxia; the most common is drowning, with or without aspiration of water. Hypoxia also may develop as a result of carbon monoxide contamination of the breathing gas. The chance of a pregnant diver becoming hypoxic because of exercising oxygen debt is unlikely.

There are few studies of the effects of fetal hypoxia or asphyxia on fetal hemodynamics. Dawes et al. (1969) reportedly found that in lower primates fetal resistance to hypoxia is much stronger than the mother's. Rankin (unpublished observations) reports that this also is true with sheep. This finding is not surprising since it is well known that the newborn infant has a strong diving reflex. Further, the leftward shift of the fetal oxygen dissociation curve provides additional defense against low $PO_2$.

Although it is true that the fetus is equipped to survive a level of hypoxia that might kill the mother, serious intra-uterine hypoxia or asphyxia may have catastrophic consequences. Sundell (unpublished observations) believes that nearly all infants who present with hyaline membrane disease have previously suffered intra-uterine asphyxia; he noted the many instances in which full-term babies exposed to massive asphyxia develop cerebral edema and multiple organ damage. He stated at the workshop that his studies with sheep have confirmed these observations. This researcher reported that when the uterine artery blood flow was significantly lowered, it produced hypoxia and acidemia in the fetus. Further, at the end of gestation, nearly 50% of the lambs so insulted in utero developed hyaline membrane disease, although none of the controls presented with this disorder (unpublished observations).

A question that should be asked is how a diving mammal's uterine artery responds to the diving reflex. Cefalo (unpublished observations) noted that redistribution of the blood caused by this reflex in the diving mammal also reduces flow in the uterine artery. However, the rather large physiological differences in oxygen metabolism between diving mammals and humans preclude close comparisons.

Panel members felt that every effort should be made during pregnancy to avoid impairing the fetal circulation. It seems clear that mild fetal hypoxia or a small change in ductus or pulmonary blood flows is probably not dangerous to the normal fetus. However, there is insufficient experimental or clinical evidence to predict the degree of change in uterine artery blood flow and ductus shunting caused by slight changes during the time the mother is submerged while breathing air. If maternal hypoxia has been severe, administering pure oxygen at sea level or at hyperbaric levels should be contemplated. Indeed, Kindwall (1978) states that hyperbaric oxygen at 3 ATA is the treatment of choice in cases of carbon monoxide poisoning. Such treatment has four important effects. First, it increases oxygen delivery to the tissues by increasing dissolved oxygen in plasma. Second, the half-time of carboxyhemoglobin is reduced from 5 hours (when breathing air) to 23 minutes if breathing oxygen at 3 ATA. Third, it reduces the damage caused by inactivation of tissue cytochrome oxydase $a_3$. Fourth, it reduces cerebral edema.

*4. Is the fetus at greater risk of decompression sickness than its mother?*

(A summary of the studies related to pregnancy and decompression sickness was presented at the beginning of this report.) Briefly, results are conflicting. McIver (1968) and Chen (1974) show that in the dog and rat the near-term fetus is more resistant to the development of circulating bubbles than is the mother. The preliminary work by Fife et al. (1978) indicates that the fetus is more vulnerable to decompression sickness than the mother.

It would be useful to clarify definitions that have caused confusion in all of these studies. First, as pointed out by Greene (unpublished observations), the term *decompression sickness* refers specifically to certain clinical symptoms, which do not include circulating bubbles. It is widely recognized that often in an adult, circulating bubbles can be detected when there is no pain or neuropathy. Second, recent unpublished studies by Fife and his co-workers now reveal that this group's initial failure to detect circulating bubbles in the mother can be accounted for by the choice of veins (Fife et al. 1978). When the Doppler detector was placed around the inferior vena cava, intravascular bubbles were detected after dives to 60 feet for bottom times as short as 2.5 minutes. Still, no bubbles were detected in the arterial system of the mother and no clinical symptoms of decompression sickness were manifested. On the other hand, many of these dives, which produced massive circulating bubbles in the fetus did not cause clinical symptoms in the dam. Thus, it is valid to conclude that the fetus is more susceptible than the mother to decompression sickness if circulating bubbles in the fetus are compared to clinical symptoms in the mother. This comparison is reasonable since the adult lung normally acts as a bubble filter, preventing gas bubbles from reaching the arterial side. On the other hand, any bubble found in the fetus' venous system has a clear pathway to the arterial side via the patent foramen ovale. Thus, circulating gas bubbles in the fetus must be considered *prima facie* evidence of arterial gas emboli. If this argument is valid, the Fife group's studies clearly suggest that, for the dive depths and times tested, the fetus is more vulnerable to decompression sickness than the mother.

Two recent and paradoxical series of observations by the Fife group further confuse the issue. The first study involved exposing twin sheep fetuses to a simulated dive: one fetus was instrumented with an ultrasonic flowmeter around an umbilical artery, while the other fetus was untouched. The instrumented fetus developed bubbles, whereupon the pregnant mother was treated on a U.S. Navy Table 5. After treatment, no bubbles were detected ultrasonically in the instrumented fetus. Twenty-four hours later, the twins were delivered prematurely, and it was found that the instrumented lamb was born dead. Autopsy revealed massive disseminated intravascular bubbles. Its twin also died during birth, but the exact cause of death was unknown: it revealed no bubbles visible to the eye. This raised the question of whether the surgical procedure itself increased the susceptibility of the fetus to decompression sickness. For this reason, the preparation used will be described in detail.

In these studies, the circulatory system of the fetus was not violated except as that may have occurred when the uterus and amnionic sac were entered. No catheters were implanted and no cotyledons were damaged. The ultrasonic Doppler transducer was loosely placed around one of the umbilical arteries, and the vessel was then replaced in its sheath. There was no indication that this vessel became constricted.

At no time after surgery was there any indication that umbilical artery blood flow had been reduced by the transducer. To be sure that the ultrasonic pulses were not creating the bubbles, an effort was made to produce bubbles *in vitro* in supersaturated plasma, using a Doppler transducer. No bubbles could be generated.

In the second study, a sheep in the early trimester was subjected to two dives to 100 fsw for 25 minutes. These dives were separated by a 24-hour rest. This sheep had been subjected to no surgery and, except for the dives, was not handled. Seventy-two hours after the second dive, this sheep spontaneously aborted a dead fetus. Autopsy revealed that the fetus contained massive disseminated intravascular gas bubbles, which were the probable cause of death. It was estimated from histological studies that some tissues died as early as 8 hours after the second dive, while others may have survived as long as 48 hours. Although this finding merits further study, it would appear that the first dive was not fatal to the fetus but that the second dive was. It cannot yet be determined if both dives contributed directly to the death of the fetus or if residual bubbles from the first dive promoted the development of lethal bubbles during the second dive 48 hours later. The possibility that repetitive dives, even after a 48-hour rest, may increase the risk of bubbles in the fetus must be considered.

The broadest and most pertinent study of the effects of diving on pregnant women is the questionnaire survey conducted by Bolton (1979). Although most of the pregnant women surveyed dived to an average depth of 45 fsw (13.7 m), many reported diving to depths in excess of 100 fsw (30.4 m) during the first trimester. The frequency of anomalies was significantly higher among these who dived while pregnant; abnormalities included hypertrophic pyloric stenosis, possible aortic coarctation, multiple hemivertebrae, ventricular septal defect, and missing right hand.

## Summary

Much of the experimental work described in this report is preliminary and requires re-evaluation and further research. A number of questions remain unanswered. Some of them are:

a. Do sheep fetuses develop circulating bubbles before the mother develops clinical symptoms of decompression sickness?

b. Can results of the sheep studies be extrapolated to humans?

c. Did the surgery or the ultrasound predispose the fetus to bubbles?

The Panel recognizes the preliminary nature of the evidence presented at and subsequent to the workshop, concerning fetal susceptibility to decompression sickness. On the other hand, the potential consequences of creating bubbles in the fetal circulation are so serious that a responsible woman should avoid any action that might precipitate them. Panel members therefore felt strongly that pregnant women should be discouraged from diving at all, until it can be shown not to risk the fetus.

## Concluding Recommendations

The panel members unanimously agreed to the following six recommendations:

1. There is no contraindication to diving for the normal, healthy non-pregnant female. The same general health criteria should apply to both male and female divers.

2. The fetus may be at greater risk than the diving mother. The potential risk primarily consists of decompression sickness, but hyperoxia, hypoxia, hypercapnia, and asphyxia may also be involved.

3. There is insufficient experimental evidence at this time to establish diving depth and time profiles that are definitely not hazardous to the human fetus Although a large number of women have dived while pregnant, results of epidemiological studies on the fetal effects of these dives on the fetuses have not yet been thoroughly analyzed.

4. The number of unanswered questions about the effects of diving on the human fetus should encourage physicians to inform their patients of the potential risks and to advise them to act in the most conservative manner.

5. Pregnant women who choose to dive against medical advice should be informed that the potential risk to the fetus apparently increases as the no-decompression limits are approached, as the oxygen tension of the inspired gas increases, and perhaps also as a function of other factors that remain to be identified.

6. Until further studies are made, we recommend that women who are or may be pregnant not dive.

## References


Assali, N.S., T.H. Kirschbaum, and P.V. Dilts, 1968. Effects of hyperbaric oxygen on uteroplacental and fetal circulation. Circulation Res. 22:573-588.

Assali, N.S., J.A. Morris, R.W. Smith, and W.A. Manson, 1963. Studies on ductus arteriosus circulation. Circulation Res. 13:478-489.

Althabe, O., R.L. Schwartz, S.V. Psoe, L. Escarena, and R. Caldero-Barcia, 1967. Effects of fetal heart rate and fetal $PO_2$ on oxygen administration to the mother. Am. J. Obst. Gynecol. 98: 858-870.

Bangasser, S. 1979. The physiology of the diving woman. Paper presented at the Undersea Medical Society Annual Scientific Meeting, Key Biscayne, Florida.

Bassett, B. 1977. Decompression sickness in female students exposed to altitude during physiological training. Paper presented at the 44th Annual Scientific Meeting of the Aerospace Medical Association, Las Vegas, Nevada.

Berman, W., R.C. Goodlin, M.A. Heymann, and A.M. Rudolph. 1975. Relationship between pressure and flow in the umbilical and uterine circulations of the sheep. Circulation Res. 38:262-266

Bolton, Margie E. 1979. The diving habits and obstetric course of pregnant scuba divers. Unpublished Master's Thesis, University of Florida, Gainsville.

Boycott, A.E., J.B.S. Haldane, and G.C.C. Damant, 1908. The prevention of compressed air illness. J. Hygiene (Cambridge 8:419-420.

Brown, Stephen D. 1979. Comparison of fetal and maternal susceptibility to decompression sickness. Unpublished Master's Thesis, Texas A&M University.

Chen, V. 1974. The prophylactic therapeutic treatment of decompression sickness by heparin and aspirin. Unpublished Master's Thesis, Texas A&M University.

Cook, C.D., P.A. Drinker, H.N. Jacobson, H. Levison, and L.B. Strang, 1963. Control of pulmonary blood flow in the fetal and newly born lamb. J. Physiol. 169:10-29.

Dawes, G.S., S.L.B. Duncan, B.V. Lewis, C.L. Merlett, J.B. Owen-Thomas, and J.T. Reeves, 1969. Hypoxemia and aortic chemoreception function in foetal lambs. J. Physiol. 201:105-116.

Ferm, V.H. 1964. Teratogenic effects of hyperbaric oxygen. Proc. Soc. Exp. Biol. Med. 116:975-976.

Fife, W.P., C. Simmang, and J.V. Kitzman, 1978. Susceptibility of fetal sheep to acute decompression sickness. Undersea Biomed. Res. 5:287-292.

Fujikura, T. 1964. Retrolental fibroplasia and prematurity in newborn rabbits induced by maternal hyperoxia. Am. J. Obst. Gynecol. 90:854-858.

Greene, K.M. 1975. Pregnancy and Diving. Pressure 4:8-9, Undersea Medical Society.

Kirschbaum, T.H., W.E. Lucas, J.C. DeHaven, and N.S. Assali, 1967. The dynamics of placental oxygen transfer. Am. J. Obst. Gynecol. 98:429-443.

McIver, R.G. 1968. Bends resistance in the fetus. Paper presented at the 1968 Annual Scientific Meeting, Aerospace Medical Association, Bal Harbor, Florida.

Miller, P.D., I.R. Telford, and G.R. Hass, 1971. Effect of hyperbaric oxygen on cardiogenesis in the rat. Biol. Neonate 17:44-52.

Pizzarello, A.J., and A.C. Shircliffe, 1967. Hyperbaric oxygen: toxic effects in chick embryos. Am. Surg. 33:958-959.

Rahn, H., Ed. 1965. Physiology of breath-hold diving and the Ama of Japan. National Academy of Sciences, Washington, D.C.

Telford, I.R., P.D. Miller, and G.F. Haas, 1969. Hyperbaric oxygen causes fetal wastage in rats. Lancet 2:220-221.

# A P P E N D I X E S

## Issues and Comments

W. P. Fife

1. Compare bends susceptibility of human and sheep fetuses.

   <u>Comment</u>: It is necessary to find an animal model that will make it possible to determine the safe depth to which a pregnant woman diver can dive without placing her fetus at risk. This might be done by conducting physiological studies of placental handling of gas transfer.

   <u>Possible Method</u>:

   1) Employ hydrogen as the inert gas.
   2) Measure fetal and uterine blood flows under various stresses in both species.

2. Determine, quantitatively, the depths and times for creation of fetal decompression sickness in the sheep or primate at early, mid, and late gestation.

   <u>Comment</u>: Currently available data only deal with the near-term fetus. It is necessary to determine bends threshold depths and times for periods ranging from implantation to mid-term.

   <u>Possible Method</u>:

   It may be possible to carry out simulated dives on a significant number of sheep at three stages of gestation, and then following them to term. The fetus would be studied for developmental abnormalities.

3. Study the effects of elevated inspired $PO_2$ on fetal circulation.

   <u>Comment</u>: There is concern over the possibility that the raised inspired $PO_2$ from air diving or from hyperbaric oxygen treatment might result in closure of the ductus arteriosus. This could in turn cause right heart hypertrophy or failure in the fetus. Further, the question of whether such shutdown is reversible was raised.

4. Investigate the effect of stress on uterine blood flow.

   <u>Comment</u>: It is known that catecholamines may reduce or shut down uterine blood flow; this phenomenon needs to be quantified in the pregnant diver.

Possible Method:

It might be possible to use chronically implanted Doppler or electromagnetic flowmeters on sheep or goats.

5. Determine the fetal response to cold water, violent exercise, or other diving-related environmental exposures.

Comment: At present no studies quantify an apparently healthy fetal response to an apparently uncomplicated dive conducted by an apparently healthy mother. It is necessary to establish normal parameters before the abnormal or detrimental effects of diving on the fetus can be assessed.

6. Determine the effects, if any, of oral contraceptives or other medication on the bends susceptibility of the female diver.

Comment: There are no definitive studies showing whether oral contraceptives increase the susceptibility of the female diver to bends. Further, little is known about the effects of many common drugs when these are administered under hyperbaric conditions.

Possible Method of Study:

Methods might involve administering estrogens and progesterones to animals, and then conducting careful decompression studies with proper controls. The question of simple bends could be studied in this way but psychotropic drugs probably would require other methods.

7. Study the relationship between increased inspired $PO_2$ and retrolental fibroplasia.

Comment: Theoretically, inspiration of 40% oxygen could cause retrolental fibroplasia in the fetus, although this effect has not been demonstrated in humans.

Possible Method of Study:

Efforts should be made to measure fetal arterial $PO_2$ when the mother is inspiring various levels of $PO_2$. This effect then could be correlated with any subsequent development of retrolental fibroplasia. Dogs, sheep, or goats could be used for these studies.

8. Determine the importance of the patent foramen ovale in fetal decompression sickness.

Comment: The foramen ovale is patent throughout most of gestation. During this time the fetal lung provides no filtration for venous gas bubbles. As a result, any venous gas emboli cross over from the right ventricle to the left ventricle, becoming arterial gas emboli. The potential for tissue ischemia and abnormal development would seem theoretically to be great under such circumstances.

9. Investigate the possible effect of diving on maturation of the ovum, ovulation, ovum transport through the Fallopian tube, fertilization, and implantation.

Comment: It is clear that female physiology is a continuously changing process, because of the significant and continual changes in female hormone balance. Virtually nothing is known of the effects that diving or the hyperbaric environment have on these hormonal processes, or the possible changes which these hormones have on female susceptibility to bends. Hormonal control of fluid and electrolyte balance is only one of the more obvious of these effects.

10. Determine what changes, if any, in female performance (problem-solving, coping with stress) during various portions of the menstrual cycle might affect diving performance.

11. Carry out epidemiological studies with women divers as subjects.

## Diving-in-Pregnancy Research Possibilities

J. R. Willson

Since little is known about the effects of hyperbaric conditions on the reproductive functions of women, it seems important that the entire process of menstruation, fertilization, implantation, development of the embryo and fetus, pregnancy and labor be studied.

### Menstruation

Normal menstruation is an orderly progression of physiologic events that includes maturation of the ovum, ovulation, transport of the ovum through the Fallopian tube, and, if it is fertilized, implantation of the developing embryo in the hormone-prepared endometrium. The principal structures involved are the hypothalamus (gonadotropin-releasing hormones), anterior pituitary (FSH and LH), the ovary (estrogen, progesterone, and the ovum), and the uterus. The process is a dynamic one, with the concentration of reproductive hormones changing daily. Uterine blood flow, fluid and electrolyte content, muscle activity, and endometrial histology and function changes cyclically in response to the rise and fall in ovarian hormone concentrations.

There are significant changes in general physiologic functions in response to the changing concentrations of estrogen and progesterone. The most obvious one is in fluid and electrolyte balance, but renal, cardiopulmonary, and vascular functions as well as others are affected.

It is well known that important mood changes occur during the menstrual cycle. Women are more likely to commit suicide or violent crimes just before or during menstruation than at any other time. The content of dreams can be correlated to the phase of the menstrual cycle. These changes are related, at least in part, to changing concentrations of estrogen and progesterone. Progesterone has a sedative and depressant effect; in fact, in large enough doses, it acts as an anesthetic.

### Proposed Studies

Normal women from whom informed consent has been obtained and who are taking no drugs or hormones and have regular ovulatory cycles could be studied during two control cycles and during two or more treatment cycles.

1. <u>Reproductive Hormone Studies</u>

A base line could be established by daily assays of FSH, LH, prolactin, estrogen, and progesterone throughout the control cycles. At least once a week, assays would be performed every three or four hours during a 24-hour period. The anterior pituitary hormones are secreted in a pulsatile fashion, and therefore it is important to have a normal base to compare with the concentrations of these substances during and after a dive.

During the treatment cycles, the subjects would be subjected periodically to hyperbaric conditions. The frequency, maximum pressure, and length of exposure should be the same during an entire cycle, but could be varied from month to month. Dives to several depths should be studied if significant changes are detected at a basic depth of 165 feet.

At least two dives should be planned during each week of the menstrual cycle to determine the effects of increased pressure on reproductive hormone secretion. Daily hormone assays would be increased during and after decompression. Samples would be obtained before compression, at the beginning of decompression, and several times during the first 24 hours after decompression. These values would then be compared to those obtained during control studies at similar phases of normal menstrual cycles.

2. Effects of Oral Contraceptives

Oral contraceptives contain synthetic estrogens and progestogens that alter several important physiologic functions. Pituitary production of FSH and LH are inhibited, probably because of a suppressive effect of the drug on the hypothalamus. This in turn inhibits ovarian hormone secretion and ovulation.

Studies could be continued on the subjects used to study the normal menstrual cycle. Since oral contraceptives inhibit hypothalamic secretion of the releasing factors and anterior pituitary FSH and LH, the secretion of ovarian estrogen and progesterone does not rise and fall as it does during the normal cycle. Daily hormone assays would therefore be non-productive. More important would be studies on performance, mood, and general physiologic functions under pressure.

3. Performance

Mental and physical problem-solving can be altered by the changing concentration of ovarian hormones during the normal menstrual cycle. This is particularly true of progesterone. Significant changes in reasoning, reaction, and performance at any stage of the cycle might be important in both sport and commercial diving.

Problem-solving, reaction time, and gross and fine physical skills could be measured twice weekly during two control menstrual cycles, during exposure to pressure at various stages of the menstrual cycle, and in women using oral contraceptives.

4. Mood

Mood swings during the cycle are well known. A significant percentage of women become very irritable during the few days before menstruation begins. Others are severely depressed and a small percentage are almost incapacitated at this time. Psychoanalysts can determine the stage of the menstrual cycle with reasonable accuracy on the basis of mood changes and dream content. The reasons for these mood swings have not been determined precisely, but they undoubtedly are related to changes in physiologic functions in response to progesterone or other hormones.

Psychologic studies could be performed at intervals throughout the cycle and correlated with the changes in hormone secretion. The effects of pressure on mood at the time of the dive could be determined and compared with studies conducted at comparable phases of control cycles.

5. Effects of Exogenous Hormones

Studies like those during the normal menstrual cycle could be performed on subjects taking exogenous hormones. Post-menopausal or castrate women who are secreting little or no ovarian estrogen could be studied during control periods and during and after exposure to hyperbaric conditions. These investigations could then be repeated after administration of estrogen and estrogen-progesterone combinations.

6. Cardiopulmonary Function and Gas Transport

Various aspects of cardiopulmonary function and gas transport could be measured during the phases of the normal menstrual cycle, during cycles in which the subjects were exposed periodically to increased pressure, in normal women taking oral contraceptives, and in castrates before and after treatment with estrogen and estrogen-progesterone combinations.

7. Effects on Other Hormones

The effects of hyperbaric exposure during various phases of the menstrual cycle on non-gonadal hypothalamic-pituitary secretory functions, on antidiuretic factors, on adrenal cortical hormone secretion, and on catacholamine synthesis could be studied in a manner comparable to that suggested above for normal reproductive hormone secretion studies.

8. Effects on Plasma Volume, Blood Constituents and Blood Clotting

In both humans and experimental animals, exposure to pressure alters plasma volume, red blood cell counts, and the blood clotting mechanism, at least temporarily. It is important to determine whether there are differences in the effects of pressure on these factors during the normal menstrual cycle and in women taking oral contraceptives or other reproductive hormones.

9. Dysmenorrhea

Dysmenorrhea varies from mild cramps to disabling, prostrating pain associated with nausea and vomiting. The pain is probably due to altered uterine contractions, with consequent effects on uterine blood flow. Presumably the pain is related to excessive prostaglandin production. Airline stewardesses often report relief from dysmenorrhea at altitudes, and the return of cramps on landing. Whether this effect is due to differences in atmospheric pressure or to the fact that these women are preoccupied with their jobs while in flight has not been determined.

Studies of the effects of pressure on uterine muscle activity and on prostoglandin production could be correlated with other studies of the menstrual cycle. It also would be interesting to learn whether pressure has any effect on the pain itself.

## Pregnancy

There is little factual information concerning the effects of diving on pregnancy. As more and more women become involved in sport and commercial diving, it becomes increasingly important that studies designed to determine the effects of exposure to hyperbaric conditions be initiated. These include the effects of pressure on tubal transport of ova and spermatozoa, on uterine implantation of the fertilized ovum, on the early differentiation of the embryo, and on the subsequent development of the fetus.

Pregnancy is a dynamic physiologic state during which there are progressive changes in maternal cardiovascular, renal, and pulmonary functions; significant changes in plasma volume and the qualitative constituents of blood; expansion of extravascular fluid volume; significent changes in the functioning of endocrine glands and progressive enlargement of the uterus, with consequent effects on posture and blood flow through the lower part of the body. The fetus is dependent upon the physiologic responses of the maternal structures for its growth and development.

There is a vast amount of information concerning both fetal and maternal physiologic functions during pregnancy in human beings and in experimental animals. Many of the techniques that have been developed could be applied to the study of pregnancy and hyperbaric conditions.

1. Fertilization and Ovum Transport

Ovum transport through the Fallopian tubes has been studied extensively in experimental animals, particularly rabbis and primates. Multiple ovulations could be induced and, using techniques already developed, the speed with which the ova are transported to the uterus could be measured. Fertilized ova could then be recovered and grown in culture.

The effects of pressure on ovulation, ovum transport, fertilization, and the early segmentation of fertilized ova could be studied in control animals and under hyperbaric conditions.

2. Implantation and Early Embryonic Development

The time and mechanism of implantation of the embryo and its early development have been studied extensively. The studies suggested above could be continued into the early stages of pregnancy, with examination of implantation sites and of the early embryo at various stages of development in control and pressurized animals.

Information concerning the effects of pressure on embryonic and fetal development could be obtained by exposing experimental animals to pressure continuously or periodically from the time of fertilization until delivery.

3. Reproductive Hormone Secretions

The effects of an intermittent or continuous hyperbaric atmosphere on estrogen, progesterone, chorionic gonadotropin, somatomammotropin, prolactin, and other hormones produced by the interaction of mother, fetus, and placenta could be studied throughout pregnancy and compared to similar assays in normal control animals.

4. Blood and Its Constituents

Plasma volume, red blood cell mass, and total hemoglobin increase during pregnancy, but hematocrit decreases because the plasma volume expands more rapidly than do the cellular constituents in blood. Serum albumin is decreased but the globulins are increased. The principal reason for these changes is the tremendous expansion of blood vessels in the developing uterus and in the vascular space that develops at the placental site through which maternal-fetal exchange is conducted.

Significant alterations in plasma volume may affect uterine perfusion and the welfare of the fetus, which is dependent upon adequate blood flow through the choriodecidual spaces for its existence. Significant decreases in maternal hemoglobin could alter gas exchange across the placenta between the mother and the fetus.

The effects of hyperbaric exposure on plasma volume proteins and the blood cells could be determined in experimental animals at various stages of pregnancy and then compared with responses of controls.

5. Blood Clotting

The effects of a hyperbaric atmosphere on the various blood factors concerned with clotting and on platelet formation, destruction, and aggregation could be checked periodically throughout pregnancy in experimental animals and then be compared with effects in normal controls.

6. Adrenocortical and Thyroid Functions

The thyroid and adrenocortical secretions change significantly during pregnancy. Acute emotional stress in experimental animals reduces uterine blood flow by as much as one-third and causes bradycardia and hypotension in fetuses. The effects of the exposure to hyperbaric conditions on these functions at various stages of pregnancy could be determined and compared to those of normal control animals.

7. Cardiopulmonary Function

The increase in cardiac output during normal pregnancy occurs because of a rise in heart rate and increased stroke volume; the curve of cardiac output, which increases by 30 to 35% by the end of the second trimester, roughly parallels the rise of plasma volume.

Systolic arterial pressure either remains unchanged or falls slightly as pregnancy advances. Diastolic pressure falls 10-15 mmHg.

Venous pressure in the lower extremities increases during pregnancy, even in the dorsal recumbent position. Venous pressure in the upper extremities is unchanged.

Systemic vascular resistance decreases during pregnancy, probably because the uteroplacental circulation acts as a low resistance area. Blood flow through the uterine arteries must be maintained to permit adequate perfusion of the choriodecidual spaces.

Changes in pulmonary function include a progressive increase in respiratory minute volume and increased tidal volume, with decreased residual air at the end of the normal expiration. Oxygen consumption increases. Alveolar and arterial $PCO_2$ are decreased during pregnancy.

There is a vast amount of information concerning cardiopulmonary function in pregnant animals, particularly sheep, at sea level and under reduced atmospheric pressures. The techniques for measuring a variety of functions have been developed.

Appropriate studies in pregnant animals in hyperbaric environments would include those on (a) cardiac function, (b) arterial blood pressure, (c) uterine blood flow, (d) cerebral blood flow, (e) gas exchange, (f) decompression sickness, and (g) pulmonary function.

8. Renal Function

Renal plasma flow and glomerular filtration both increase during normal pregnancy. Tubular function also changes. There are changes in aldosterone production and in antidiuretic hormone secretion.

Various aspects of renal function and electrolyte metabolism could be measured in pregnant animals before, during, and after hyperbaric exposure.

9. Uterine Muscle Activity

The smooth muscles of the uterus become progressively more active as pregnancy advances. The factors responsible for the onset of premature labor and labor at term have not been completely elucidated, but variations in estrogen-progesterone concentrations, adrenocortical substances, and in the production of prostaglandins are probably the most important areas for study. The fetus probably plays an important role in determining when labor starts. For example, intrauterine fetal death is usually followed, in human beings, by the onset of labor. In some experimental animals, hypophysectomy or adrenalectomy produces prolongation of pregnancy far beyond the time when labor should have begun.

Uterine muscle activity could be measured *in vivo* and *in vitro* before, during, and after hyperbaric exposures.

Changes in electrolyte, progesterone, estrogen and prostaglandin concentrations in uterine muscle could be determined before and after exposure to hyperbaric conditions.

Changes in adrenocortical steroid production could be measured before, during, and after pressurization.

## Fetus

Techniques have been developed for long-term monitoring of a varient of physiologic functions in the fetuses of sheep, goats, monkeys, and other experimental animals.

Fetal blood pressure, umbilical artery blood flow, gas exchange, intrauterine respiratory efforts, estrogen metabolism, renal function, adrenal cortical secretion, electrolyte and acid/base balance, and a variety of other functions can be measured repeatedly as pregnancy advances. Such studies could be made before, during, and after decompression.