

# The Effects of Hypothermia in Pregnant Rats: A Preliminary Report

ROGER A. GLOVER, JR., M.D.,\* CHAN H. PARK, M.D.†  
AND FRED T. GIVEN, JR., M.D.

*Department of Obstetrics and Gynecology  
DePaul Hospital,  
Norfolk, Virginia 23505*

Our interest in the effects of hypothermia in pregnancy was aroused by the necessity of using this therapy on our obstetrical service.

A review of the literature revealed that in acute experiments, the fetal temperature fell to the same extent as that of the mother (Assali and Westin, 1962); changes in fetal O<sub>2</sub> saturation, CO<sub>2</sub> content, and pH generally followed similar changes in the maternal host (Vandewater and Paul, 1960). However, we could find only three studies of fetal survival. One, using unanesthetized guinea pigs, showed no change in fetal size or survival (Vandewater and Paul, 1960). Another, using ether anesthesia and hypothermia in mice, revealed some possible adverse effects when used early in pregnancy (Mousse, Boba, and Peck, 1961). The third showed that freezing pregnant hamsters produced death of the fetuses and also gross anomalies related to the day of gestation and duration of the procedure (Smith, 1957). Hehre (1965) reviewed the few reported cases of hypothermia during pregnancy in humans.

It appeared to us that more controlled animal studies were needed to evaluate the effects of hypothermia on fetal and neonatal survival.

## Methods

In planning and conducting this study, we realized the importance of a) defining and grading "hypothermia," b) separating teratology from fetology, and c) overcoming the shivering phenomena in the animals subjected to hypothermia.

For the classification of hypothermia, we used the criteria of Swan and Paton (1961):

Moderate hypothermia . . . . .	37—28 C
Intermediate hypothermia . . . . .	28—20 C
Deep hypothermia . . . . .	20—0 C

\* Present Address: Box 596, Abingdon, Virginia

† Department of Radiology, University of North Carolina, Chapel Hill, North Carolina

All experiments were carried out between the 17th and 19th days of gestation. At this stage of development in the fetal rat, embryogenesis is complete and teratogenesis, in the strict sense, does not occur (Wilson and Warkany, 1965).

Shivering, known to occur when the rat is subjected to hypothermia, was overcome by the use of different types of anesthesia including pentobarbital, ether, and CO<sub>2</sub> narcosis.

In evaluating the results of the experiments, we took the following factors into consideration: Maternal survival and death, fetal survival and death, litter number, stillbirths, birth weight, sex ratio, and gross malformations.

A total of 60 female rats of the Sherin Wistar Strain, weighing 220-240 grams, were used. For purposes of evaluation, no experiments were conducted until the rats had been maintained through two generations. All females were bred to the same male. The first breeding was used to insure fertility, while the second breeding served as a control or experiment. All were maintained on Purina Lab Chow and water ad libitum in a controlled temperature of 72 F. During the experiments, temperatures were measured with a rectal probe and telethermometer (Yellow Springs Ins. Co.).

All rats were bred for three days and pregnancy was diagnosed by palpation. Those rats which had not delivered by the expected day were sacrificed; pregnancy was confirmed in each rat by the finding of metrial glands. All stillborn fetuses were examined after being fixed in Bouin's solution. The animals were divided into six groups:

- Group C-1 Twelve pregnant rats served as the first group of controls.
- Group C-2 Twelve pregnant rats were given pentobarbital (30 mg/kg). These served as a second set of controls.
- Group E-1 Six pregnant rats were given pentobarbital (30 mg/kg), and cooled by ice water immersion. Their rectal temperatures were maintained at 28-30 C for two hours.
- Group E-2 Eight pregnant rats were given pentobarbital (30 mg/kg), and cooled by ice water immersion to 28-30 C for four hours.
- Group E-3 Six pregnant rats were given open drop ether anesthesia, and cooled by ice water immersion to 28-30 C for four hours.
- Group E-4 Four pregnant rats were given open drop ether anesthesia, and cooled by ice water immersion to 22-24 C for two hours.

Group E-5 Six pregnant rats were given pentobarbital (30 mg/kg), and cooled by ice water immersion to 22-24 C for two hours.

Group E-6 Six pregnant rats were subjected to the closed container technique of cooling (CO<sub>2</sub> narcosis) (Andjus, 1956). The temperature was lowered to 16-18 C by placing them in a hermetically sealed, 1 liter jar at 2 C for two hours.

### Results









No gross anomalies or changes in sex ratio were noted in any experimental group. The findings are shown in the Table. There were no adverse effects noted in the experimental groups, E-1, E-3, E-4, or E-6. In group E-2, use of moderate hypothermia for four hours with pentobarbital anesthesia resulted in only one live-born fetus. The rest were either resorbed or stillborn. This deleterious effect was not noted if the

same conditions were kept for only two hours (group E-1). Intermediate hypothermia and pentobarbital anesthesia (group E-5) resulted in five of the six animals dying during the experiment, possibly in ventricular fibrillation (Blair, 1964; Covino and Charleson, 1954). Only one animal survived the experiment, and it delivered nine stillborn fetuses.

### Comments

The results of this small series of experiments suggest that the use of hypothermia with ether anesthesia (for what may be considered relatively prolonged periods in relation to the gestation period of a rat) causes no harmful effects in the fetus, even if carried to depths of hypothermia rarely used clinically. That the duration of the experiment can be important was noted when cooling and pentobarbital were used for four hours (group E-2). In this instance, there were disastrous effects on fetal survival, whereas when the experiment lasted for two hours no harmful effects

## EFFECTS OF HYPOTHERMIA ON GRAVID RATS

Group	Control		Experimental					
								
	C-1	C-2	E-1	E-2	E-3	E-4	E-5	E-6
Number of Animals in Group	12	12	6	8(5)*	6	4	6(1)⊕	6
Temperature (°C)	37.5	37.5	28-30 M O D E R A T E			22-24 I N T E R M E D I A T E		16-18 D E E P
Duration of Cooling (hrs.)	0	4	2	4	4	2	2	2
Anesthesia	0	PENTO-BARBIT.	PENTO-BARBIT.	PENTO-BARBIT.	ETHER	ETHER	PENTO-BARBIT.	CO <sub>2</sub>
Number of Live-Born	111	99	59	1	57	40	0	48
Number of Stillborn	8	5	3	10	2	1	9	3
Average Litter	9.9	8.7	10.3	3.7	9.8	10.1	9	8.5
Average Weight—Live and Stillborn	6.1	6.1	6.1	4.5*	6	5.9	4.3*	6.1
* IN FIVE ANIMALS PREGNANCY WAS CONFIRMED BY METRIAL GLANDS								
⊕ FIVE ANIMALS WERE KILLED BY EXPERIMENT								
* SIGNIFICANTLY DIFFERENT FROM CONTROL (p<0.001)								

were noted. It is clear that in order to fully evaluate the safety of a given anesthetic agent used to overcome shivering, further studies are required in which the time factor is varied.

The death of five out of six mothers in group E-5 might have been due to ventricular fibrillation. Blair (1964) and Covino and Charleson (1954) reported a higher incidence of ventricular fibrillation at temperatures below 25 C with pentobarbital than with ether anesthesia.

One of the more interesting results was the lack of harmful effects from the combination of deep hypothermia and CO<sub>2</sub> narcosis (group E-6). One might speculate that this would fit in with the finding by Miller and Miller (1966) that hypothermia and hypoxia-hypercapnia protect the fetus and maternal host. These preliminary results need to be confirmed and amplified by further experimentation. Similar studies, performed in the teratogenic phase of the embryo, also seem indicated.

### Summary

We have evaluated the effects of varying degrees and durations of hypothermia, combined with anesthesia, on pregnant rats of the Sherin Wistar Strain. Moderate (surgical) and intermediate hypothermia, with ether anesthesia, were safe for both fetus and mother. With pentobarbital anesthesia, however, there were harmful effects, depending on the depth and duration of hypothermia; moderate hypothermia increased fetal mortality, and intermediate hypothermia increased fetal and maternal mortality. The combination of CO<sub>2</sub> narcosis and deep hypothermia induced no ill effects.

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