Energy balance and brown adipose tissue thermogenesis during pregnancy in Syrian hamsters

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WADE, GEORGE N., GRAHAM JENNINGS, AND PAUL TRAYHURN. *Energy balance and brown adipose tissue thermogenesis during pregnancy in Syrian hamsters.* Am. J. Physiol. 250 (Regulatory Integrative Comp. Physiol. 19): R845–R850, 1986.—Energy balance and brown adipose tissue thermogenesis were examined during pregnancy in Syrian hamsters (*Mesocricetus auratus*). Neither estrous cycles nor pregnancy had any effect on food intake, but both were accompanied by significant changes in body weight. Despite their substantial weight gains (attributable to growth of fetuses and placentas), pregnant hamsters actually lost a mean of 48 kJ in carcass energy, whereas unmated controls gained 98 kJ over the same 15 days. During pregnancy hamsters exhibited an increase in protein deposition (almost entirely in the fetuses and placentas), but they lost nearly 40% of their body lipid. An apparent increase in energy expenditure occurred despite a highly significant decrease in brown adipose tissue thermogenesis during pregnancy. By *day 15* of pregnancy (within 13 h of expected parturition) there were substantial decreases in interscapular brown adipose tissue weight (−59%), protein content (−54%), and cytochrome-*c* oxidase activity (−69%). These changes in brown adipose tissue were evident by *day 4* of pregnancy and persisted through lactation. It is suggested that this suppression of brown adipose tissue function is due to increased circulating levels of prolactin and subsequently to the nutritional stress of conceptus growth in the absence of an increase in food intake.

food intake; body weight; carcass composition; estrous cycles; metabolic efficiency; lactation; prolactin

THERE IS A CONTINUING INTEREST in energy metabolism during pregnancy, both in human beings and in experimental animals. In most mammalian species, pregnancy is associated with a substantial maternal weight gain in addition to the growth of the fetus(es) and placenta(s). Carcass analyses have revealed that much of this maternal weight gain is due to increased deposition of lipid in white adipose tissues (16, 19, 25). The lipid stored during pregnancy is then mobilized to meet the increased energy demands of lactation (25). The enhanced storage of energy as lipid is typically associated with a significant increase in food intake. For example, rats and mice increase their caloric intakes by 40–100% during the latter part of pregnancy (16, 19, 25). In addition to this hyperphagia, it has been suggested that there is an increase in metabolic efficiency during pregnancy in rats (17). Thus it is possible that a decrease in energy expenditure could contribute to the enhanced energy storage. Voluntary exercise is known to be decreased in pregnancy (24), and a reduction in brown adipose tissue thermogenesis could also contribute to energy savings. Brown adipose tissue is an important energy-expending tissue in rodents, and several types of obesity may be due, at least in part, to decreased thermogenesis in this tissue (22, 29).

However, a recent study in which pregnant mice were prevented from overeating indicates that there is no overall increase in metabolic efficiency during pregnancy (19), suggesting that at least in mice the increased energy storage of ad libitum-fed pregnant animals is attributable entirely to their hyperphagia. Consistent with this view is the finding that although brown adipose tissue is clearly thermogenically inactive during lactation (10, 28), there appears to be no decrease in thermogenesis in the tissue until the very end of pregnancy in both rats and mice (2, 26), i.e., not until after most of the extra energy storage has taken place.

In the experiments reported here we examined energy balance and brown adipose tissue function during pregnancy in Syrian hamsters (*Mesocricetus auratus*). Hamsters were considered to be an ideal species for investigating the energetics of pregnancy, particularly energetic adaptations, because they do not increase their food intake while pregnant (6, 7, 32). Although it has been suggested that hamsters do not store excess energy during pregnancy (6, 7), we are not aware of any published studies directly measuring body composition or energy balance in pregnant animals of this species. Hamsters have well-developed brown adipose tissue that is responsive to nutritional and environmental influences (3, 30), and although thermogenic activity has not been measured, there is evidence that brown adipose tissue weight is considerably reduced during pregnancy in hamsters (27).

MATERIALS AND METHODS

Animals and Housing

Female Syrian hamsters of the outbred DSN strain, weighing 70–80 g, were purchased from Intersimian (Abingdon, Oxon, UK) and housed singly in wire-mesh cages. Tap water and food pellets (LAD-1, Scientific Feeds, K and K Greef Chemicals, Croydon, UK) were available ad libitum. The gross composition (wt/wt) of the diet was 21.3% protein, 3.4% fat, 41.8% starch, and

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2.8% sucrose, and the gross energy density was 17.2 kJ/g wet wt. Room temperature was carefully controlled at 24 ± 0.5°C, and a 14:10 light-dark cycle (lights on at 2230) was maintained.

Energy Balance and Carcass Analyses

In *experiment 1* food intake (to the nearest 0.01 g) and body weight (to the nearest 0.1 g) were measured daily at 1000. Spilled food and feces were collected on absorbent paper placed under the cages. Feces were collected throughout the experiment, and their energy content was measured to determine digestible energy intake. The digestibility of the diet (84.4%) was identical in the pregnant and unmated hamsters. Metabolizable energy intake was not measured in the study; presumably it did not differ between the two groups and was little different from the digestible energy intake (19).

Animals were killed for carcass analyses by cervical dislocation. The interscapular brown adipose tissue and parametrial white adipose tissue (left pad) were dissected and weighed; the parametrial fat pad was returned to the carcass. In the pregnant animals the uterine contents were weighed and processed separately. The gut contents were removed, and the carcasses and uterine contents were autoclaved at 10^4 kg/m^2 for 50 min in order to soften the tissues. They were then homogenized in an equal weight of water and freeze-dried. The energy contents of the carcasses, uterine contents, feces, and diet were determined by bomb calorimetry using a Gallenkamp adiabatic calorimeter (model CB-100) calibrated with dry benzoic acid standards (19). Carcass lipid was determined by extracting ~500-mg samples of freeze-dried carcass with 3 × 10 ml of petroleum ether. Nitrogen was determined in duplicate 10- to 15-mg samples of the dehydrated carcass using a Carlo Erba automatic nitrogen analyzer (model 1500); protein was derived by multiplying nitrogen values by 6.25. The initial carcass energy, lipid, and protein contents of the hamsters were estimated from their body weights by reference to a baseline group of hamsters (n = 11) of identical age and weight range to the two experimental groups. The baseline hamster carcasses were processed in exactly the same way as the experimental groups.

Brown Adipose Tissue Measurements

In both experiments interscapular brown adipose tissue was rapidly dissected and weighed to the nearest 0.1 mg. The tissue was then homogenized in a medium (pH 7.2) containing 250 mM sucrose, 1 mM *N*-2-hydroxyethylpiperazine-*N'*-2-ethanesulfonic acid, and 0.2 mM EDTA (8). Aliquots of the homogenates were taken for the measurement of cytochrome-*c* oxidase (EC 1.9.3.1) activity by a spectrophotometric assay (31) and for determination of total tissue protein (8). The bulk of the homogenate was used for the isolation of mitochondria (8). The activity of the mitochondrial proton conductance pathway was assessed by a purine nucleotide binding assay (8). Freshly prepared mitochondria were incubated at room temperature for 7 min with 10 μM [^{3}H]-GDP in a medium at pH 7.1 (8). [^{3}H]GDP and [^{14}C]-sucrose were purchased from Amersham International (Amersham, Bucks, UK).

Statistical analyses

Data were analyzed using t tests or one-way analyses of variance followed by Newman-Keuls post-hoc tests and were considered statistically significant if $P < 0.05$.

Procedures

Experiment 1 examined energy balance during pregnancy. Eighteen hamsters (mean body wt 88 g) were divided into two groups (n = 9 for each) matched for base-line food intake and body weight (measured over 5 days). On the day of estrus, the animals in one group were housed with sexually active males for 6 h starting at lights out. Animals in the other group were left undisturbed. Food intake and body weight were measured until *day 15* of pregnancy (i.e., <13 h before the expected time of parturition) when they were killed by cervical dislocation. Estrous cycles were monitored in all nine unmated hamsters so that food intake and body weight changes could be correlated with the cycle. Brown adipose tissue was then processed as described above.

Experiment 2 examined the time course of the changes in brown adipose tissue during pregnancy and lactation. Female hamsters were divided into seven groups matched for base-line body weight (mean body wt 105 g). The control (n = 10) group was left undisturbed, and the remaining animals were mated as in *experiment 1*. Animals were killed at *days 4* (n = 8), *8* (n = 7), *12* (n = 7), or *15* (n = 7) of pregnancy or *days 10–11* (n = 8) or *21* (n = 8) of lactation. Brown adipose tissue was then processed as described above.

RESULTS

Experiment 1. Energy Balance

Food intake and body weight. Food intake did not vary over the estrous cycle, but there were highly significant changes in body weight gain ($P < 0.01$) (Fig. 1). All animals gained significant amounts of weight at estrus (the 24-h period during which sexual receptivity oc-

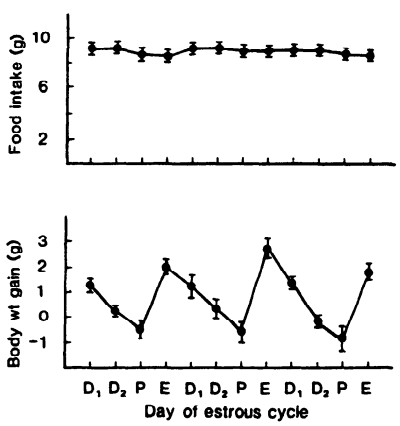

FIG. 1. Effect of estrous cycles on food intake and body weight gain in Syrian hamsters. P, proestrus; E, estrus; D_1 and D_2, first and second days of diestrus, respectively.

curred), with smaller gains during the 2 days of diestrus. Proestrus was consistently associated with small weight losses (Fig. 1).

Energy intake did not change at all during pregnancy (Fig. 2 and Table 1). Body weight changes were minimal during the first week of pregnancy, but during the second half of gestation, pregnant animals gained significantly more weight than the unmated controls (Fig. 2). However, this weight gain was entirely accounted for by the uterine contents (Table 1). The pregnant hamsters had a mean of 8.7 fetuses per animal.

Energy balance and carcass composition. During the 15 days of the experiment the control hamsters gained 98 kJ of carcass energy and had a gross efficiency (energy gain/digestible energy intake) of 5.5%. Approximately 60% of this gain could be accounted for by carcass lipid (Table 2). In contrast, the pregnant hamsters actually lost 98 kJ of carcass energy, and the 50 kJ in the fetuses and placentas only partially offset this energy loss (Table 1). The energy loss during pregnancy was due to the loss of nearly 40% of carcass lipid (Table 2), in contrast to the 15% gain in carcass lipid that occurred in the controls. These changes in total body lipid were reflected in the parametrial fat pad weights, which were reduced in the pregnant animals (Table 3). As noted previously (30), parametrial fat pad weight and total carcass lipid were found to be highly correlated ($r = 0.95$, $P < 0.01$).

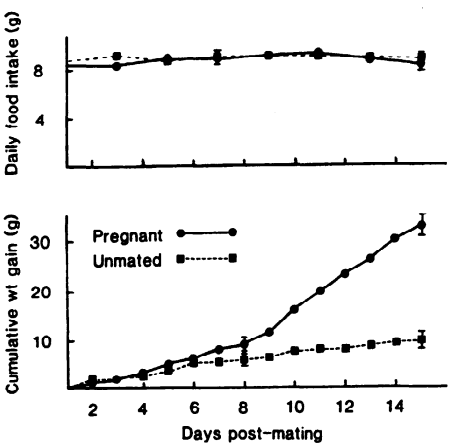

FIG. 2. Food intake and body weight gain in pregnant and unmated Syrian hamsters.

TABLE 1. *Effect of pregnancy on energy balance in Syrian hamsters*

	Unmated Control	15-day Pregnant
n	9	9
Cumulative food intake, g	123.0±4.1	121.5±3.1
Digestible energy intake, kJ	1,787±57	1,763±45
Adult female wt, g		
Initial	87.8±2.9	88.1±0.8
Final	97.4±4.0	120.8±2.8*
Gain	9.7±2.1	32.7±2.3*
Adult female energy, kJ		
Initial	742±38	747±10
Final	839±52	649±23*
Gain	98±24	−98±20*
Uterine contents		
Wt, g		23.2±2.3
Energy, kJ		50±5
No. of fetuses		8.7±0.7
Total energy gain including uterine contents, kJ	98±24	−48±19*

Values are means ± SE. *n*, number of animals. * $P < 0.001$ vs. controls.

TABLE 2. *Effect of pregnancy on carcass composition in Syrian hamsters*

	Unmated Control	15-day Pregnant
Adult female protein, g		
Initial	16.74±0.50	16.80±0.14
Final	18.41±0.90	18.65±0.30
Gain	1.67±0.30	1.84±0.31
Conceptus protein, g		1.99±0.19
Total protein gain, g	1.67±0.30	3.83±0.31*
Adult female lipid, g		
Initial	9.22±0.68	9.31±0.19
Final	10.65±1.16	5.70±0.46*
Gain	1.42±0.67	−3.61±0.39*
Conceptus lipid, g		0.15±0.01
Total lipid gain, g	1.42±0.67	−3.46±0.39*

Values are means ± SE. * $P < 0.001$ vs. controls.

TABLE 3. *Effect of pregnancy on organ weights in Syrian hamsters*

	Unmated Control	15-day Pregnant
Interscapular brown adipose tissue, mg	195±6	80±8*
Parametrial white adipose tissue‡, mg	318±46	167±12†
Liver, g	5.27±0.37	6.11±0.34

Values are means ± SE. *† $P < 0.001$ and $P < 0.01$ vs. controls, respectively. ‡ Left pad only.

TABLE 4. *Effect of pregnancy on interscapular brown adipose tissue in Syrian hamsters*

	Unmated Control	15-day Pregnant
Tissue protein content, mg	49.8±1.7	23.0±1.9*
Cytochrome-*c* oxidase activity, μmol cytochrome-*c* oxidized/min	64.0±6.2	19.6±3.5*
GDP binding, pmol/mg mitochondrial protein	345±27	347±38

Values are means ± SE. * $P < 0.001$ vs. controls.

Although there was no significant difference in maternal protein gain between pregnant and unmated control hamsters, the fetuses and placentas contained nearly 2 g protein (Table 2). Thus total protein accretion was significantly elevated in pregnancy, but nearly all (92%) of the increase was in the fetuses and placentas. The deposition of lipid in the conceptus was small (Table 2).

Brown adipose tissue. By *day 15* of pregnancy the weight of the interscapular brown fat pad was reduced by 59% compared with the unmated control animals (Table 3). This decrease in tissue mass, which has been reported previously (27), was accompanied by significant reductions in both mitochondrial content, as indicated by cytochrome-*c* oxidase activity, (−69%) and total tissue protein (−54%) (Table 4). However, mitochondrial [^{3}H]-

GDP binding (pmol bound/mg mitochondrial protein) was unaltered during pregnancy (Table 4).

Experiment 2. Time Course of Changes in Brown Adipose Tissue

As in *experiment 1*, body weight did not change significantly until the last half of pregnancy (Table 5). Body weight fell at parturition but did not change throughout lactation (Table 5). The amount of parametrial white adipose tissue began to decline early in pregnancy, but this change was not statistically significant until *day 12*. By *day 15* of pregnancy, fat pad weight was reduced by 72% (Table 5). Fat pad weight continued to decline through midlactation, but some recovery occurred by *day 21* postpartum (Table 5).

Substantial changes in brown adipose tissue were evident by *day 4* of pregnancy (Table 5). Although the level of mitochondrial [^{3}H]GDP binding was unchanged throughout pregnancy, tissue weight (−28%), protein content (−25%), and cytochrome-*c* oxidase activity (−39%) were all significantly reduced by *day 4*. No further changes occurred through *day 8*, but during the last half of pregnancy the tissue continued to regress. By *day 15* of pregnancy, tissue weight (−52%), protein content (−47%), and cytochrome-*c* oxidase activity (−64%) were reduced to levels comparable to those seen in *experiment 1*.

Brown adipose tissue remained thermogenically inactive during lactation, although some recovery in weight was evident at 21 days postpartum, as with white adipose tissue, and there was a marked increase in cytochrome-*c* oxidase activity (Table 5).

DISCUSSION

As expected from previous studies (6, 7, 32), Syrian hamsters did not exhibit any change in ad libitum food intake during pregnancy, making them an ideal species in which to study the energetics of pregnancy, particularly energetic adaptations. The results of *experiment 1* clearly indicate that there is no increase in metabolic efficiency during pregnancy in hamsters, and this is similar to the findings of a recent study in which the hyperphagia of pregnancy in mice was prevented by pair-feeding pregnant animals to the ad libitum intake of unmated controls (19). In fact, pregnant hamsters exhibited a substantial decrease in metabolic efficiency and actually lost carcass energy during gestation by depleting their lipid stores (Table 1).

It is not clear why hamsters fail to increase their food intake and do not store extra carcass lipid as other species of rodents do during pregnancy (16, 19, 25). However, it is not at all uncommon in other situations for hamsters to fail to match their food intake and short-term energy needs (3, 23, 30). Perhaps this is made possible by the extensive hoarding that is seen in hamsters (23). Indeed, hoarding is elevated during pregnancy in hamsters (6, 14). Storage of large amounts of metabolic fuels outside the body, but in a readily accessible hoard, may reduce the need for anticipatory changes in food intake (23). It is possible that food hoarding, rather than food intake, is the best measure of behavioral energy storage in hamsters. In any event, hamsters exhibit perfectly adequate reproductive performance in the absence of any preparturitional hyperphagia and fattening and will tolerate loss of body lipid as part of the normal physiological response to pregnancy. A corollary of the loss of body lipid during pregnancy in hamsters is that internal energy stores are not likely to make any real contribution to meeting the energy costs of lactation in this species.

The energy demands of conceptus protein synthesis probably account for a portion of the increased energy expenditure during pregnancy. Assuming an energy cost of 53 kJ/g of protein deposition (18), the extra 2.16 g of protein stored by the pregnant animals (Table 2) would have cost an additional 115 kJ. As in pair-fed pregnant mice (19), this increased protein deposition was accompanied by a mobilization of carcass lipid. However, the energy cost of pregnancy exceeded the requirements of enhanced protein deposition. The pregnant hamsters lost ~3.5 g of carcass lipid, whereas the unmated animals stored >1.4 g fat (Table 2), a difference of ~191 kJ [assuming an energy density of 39.2 kJ/g of carcass lipid (19)]. When the cost of lipid deposition in the controls is added [19 kJ (18)], the resulting value, 210 kJ, is

TABLE 5. *Effect of pregnancy and lactation on body weight and brown adipose tissue in Syrian hamsters*

	Unmated Control	Day of Pregnancy				Day of Lactation	
		4	8	12	15	10–11	21
n	10	8	7	7	7	8	8
Body wt, g	111.7±3.5^a	112.0±4.4^a	115.8±1.9^a	126.2±2.9^b	137.1±3.5^c	110.2±3.5^a	109.5±2.7^a
No. of fetuses/pups			11.9±0.7^a	11.3±0.8^a	9.1±0.3^b	8.6±0.6^b	6.3±0.5^c
Parametrial white adipose tissue wt, mg	362±31^a	288±59^a	298±28^a	171±17^b	103±7^c	51±7^d	123±14^c
Interscapular brown adipose tissue							
Wet wt, mg	213±13^a	153±8^{bd}	164±8^b	122±10^{cd}	102±6^c	104±13^c	137±8^d
Tissue protein content, mg	38.0±2.3^a	28.4±1.5^b	31.1±1.8^b	27.2±1.7^b	20.3±2.3^c	16.8±2.8^c	15.0±1.5^c
Cytochrome-*c* oxidase, μmol cytochrome-*c* oxidized/min	63.2±3.6^a	38.7±5.1^b	36.8±2.8^b	29.9±2.9^{bc}	22.9±2.2^{cd}	16.6±2.2^d	32.7±3.7^b
GDP binding, pmol/mg mitochondrial protein	386±29	369±19	368±19	*	401±27	475±44	443±25

Values are means ± SE. Groups with different superscripts are significantly different, $P < 0.05$. * Samples lost due to assay malfunction.

considerably in excess of the estimated cost of protein deposition. In view of this discrepancy, it is possible that the energy cost of protein deposition is greater in hamsters than the values determined in rats (18). Alternatively, other as yet unspecified energy-expending processes may be activated during pregnancy in hamsters.

Overall energy expenditure is increased in pregnant hamsters despite the energy savings achieved by significant decreases in voluntary exercise (20) and brown adipose tissue thermogenesis. In *experiment 1*, interscapular brown adipose tissue wet weight, protein content, and mitochondrial content (as indicated by tissue cytochrome-*c* oxidase activity) were all suppressed at *day 15* of pregnancy. Although mitochondrial [^{3}H]GDP binding, an index of the activity of the proton conductance pathway, was unaffected, whole tissue thermogenesis would be expected to be substantially reduced because of the ~70% reduction in tissue mitochondrial content (Table 4) by *day 15*.

Experiment 2 replicated these decreases in brown adipose tissue at the end of pregnancy and demonstrated that they were evident as early as *day 4* of gestation and continued throughout lactation. Presumably, brown adipose tissue thermogenesis must recover after weaning of the pups, and increases in both the weight of the tissue and in cytochrome-*c* oxidase activity during the second half of lactation indicate some capacity for recovery. In pregnant rats and mice, interscapular brown adipose tissue thermogenesis (assessed by mitochondrial [^{3}H]-GDP binding) is decreased only at the very end of pregnancy (2, 26). In contrast to hamsters, pregnant mice exhibit no change in cytochrome-*c* oxidase activity in brown adipose tissue, and in rats and mice fed ad libitum, tissue weight is actually raised during pregnancy, presumably due to an increase in triglyceride storage (1, 2). Even in pregnant mice restricted to the normal energy intake of unmated animals, cytochrome-*c* oxidase activity in brown adipose tissue is unaffected, and the only effect of restriction is to prevent the increase in tissue weight (2).

It is not clear what physiological signals are responsible for the thermogenic inactivity of brown adipose tissue in pregnant hamsters. Food deprivation decreases brown adipose tissue activity in several species of rodents (5, 21; Trayhurn and Jennings, unpublished data), including Syrian hamsters (I. Levin, G. N. Wade, G. Jennings, and P. Trayhurn, unpublished data). However, because significant changes are evident by *day 4* of pregnancy, it is highly unlikely that any nutritional stress caused by fetal growth is responsible, at least for the initial response. It is also unlikely that any residual effects of changes in food intake associated with mating or the estrous cycle play a role. Note that food intake did not vary with the estrous cycle (Fig. 1). In addition, the night of mating was accompanied by perfectly normal estrous weight gains (Fig. 1).

It is possible that some of the endocrine alterations of early pregnancy are directly responsible for the changes in brown adipose tissue function. Circulating progesterone levels are elevated during pregnancy, but the plasma concentration may not change rapidly enough to account for the significant suppression of brown adipose tissue by *day 4* of gestation (11). Although progestins do not affect brown adipose tissue in mice fed normal diets, progesterone may prevent the activation of brown adipose tissue thermogenesis during voluntary overfeeding (D. Richard and P. Trayhurn, unpublished data).

Prolactin may affect brown adipose tissue function in several physiological states, including pregnancy. In hamsters, circulating prolactin levels increase rapidly after mating, peak during the first half of pregnancy, and throughout lactation remain elevated above levels observed in unmated animals (4). In lactating rats, both the suppression of brown adipose tissue thermogenesis and the elevation in plasma prolactin level are proportional to the size of the litter (10, 12). In unmated rats, an elevation of circulating prolactin titers induced by ectopic pituitary transplants causes a decrease in mitochondrial GDP binding in brown adipose tissue (B. J. Moore, T. Gerardo-Gettens, J. S. Stern, and B. A. Horwitz, unpublished observations). Thus it is possible that prolactin decreases brown adipose tissue thermogenesis in several species of rodent.

It is also possible that naturally occurring decreases in circulating levels of prolactin could induce brown adipose tissue growth. In both female and male hamsters, Syrian as well as Siberian (*Phodopus sungorus sungorus*), exposure to short photoperiods is associated with a decrease in plasma prolactin levels and an increase in brown adipose tissue growth and thermogenic capacity (3, 9, 13, 30).

The suggestion that changes in hormone levels could decrease brown adipose tissue thermogenesis during pregnancy and lactation in hamsters certainly does not preclude an important role for other metabolic factors. Indeed, it is not at all unlikely that the increasing suppression of brown adipose tissue during the last half of pregnancy is due in part to the nutritional stress of fetal/placental growth in the absence of a concurrent increase in food intake. Conceivably, the inactivity of brown adipose tissue during early pregnancy is a hormone-induced anticipatory response that partially ameliorates the nutritional stress of late pregnancy.

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