

Influence of Body Condition on Reproductive Output in the Guinea Pig

CATHERINE LOUISE MICHEL* AND XAVIER BONNET
CEBC CNRS, UPR 1934, Villiers en Bois, Beauvoir sur Niort, France



ABSTRACT

Reproduction is expensive. Substantial body reserves (i.e. high body condition) are usually required for females to undertake offspring production. In many vertebrates, maternal body condition positively influences reproductive output, and emaciated individuals skip reproduction. However, the impact of extremely high body condition, more specifically obesity, on animal reproductive performance remains poorly understood and research has generated contradictory results. For instance, obesity negatively affects fertility in women, but does not influence reproductive capacity or reproductive output in laboratory rodents. We examined the influence of high body condition on reproductive status and reproductive output in the guinea pig. In captivity, when fed ad libitum, guinea pigs store large amounts of fat tissues and exhibit a tendency for obesity. Our results show that obesity negatively affected reproduction in this species: both the proportion of fertile females and litter size were lower in the fattest females. Therefore, guinea pigs may represent suitable organisms to better understand the negative effect of obesity on reproduction. *J. Exp. Zool.* 317:24–31, 2012. © 2011 Wiley Periodicals, Inc.

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Energy requirements are generally elevated in reproductive females of most animal species. Vitellogenesis, gestation, nest building, or lactation, for instance, entails high expenditure. To fulfil these demands, females often rely on various forms of resource storage, usually body reserves, and hence require a high body condition index (BCI) at the onset of the reproductive season (Bonnet et al., '98; Schulte-Hostedde et al., 2001). Many studies have demonstrated that insufficient body reserves before reproduction preclude offspring production: low body condition can inhibit folliculogenesis, ovulation, or mating behaviors (Frisch and Mc Arthur, '83; Naulleau and Bonnet, '96). In humans, the markedly low fat indexes typically recorded in professional athletes, dancers, or anorexic individuals are often associated with infertility (Vigersky et al., '77; Cumming and Rebar, '83; Frisch and Mc Arthur, '83). In livestock, domestic, and laboratory animals, pronounced meagreness and/or rapid weight loss severely perturbs fertility (Jackson, '15; Casida, '59; Kennedy and Mitra, '63; Bronson, '85).

Detailed investigations in mammals have revealed that the initiation and completion of reproduction are essentially dependent on the amounts of metabolic fuel available to the organism, reflecting the balance between body reserves, incoming resources, and energy expenditure (Glass et al., '79;

Bronson, '87, '98; Schneider and Wade, '89; Bronson and Manning, '91; Schneider et al., 2000). Apart from the impact of body reserves on reproductive processes, maternal body condition correlates positively with reproductive performances in different species: litter size (Keller and Krebs, '67; Tamarin, '77; Murie and Dobson, '87; Atkinson and Ramsay, '95), total offspring mass (Clutton-Brock et al., '82), or both (Myers and Master, '83; Dobson and Myers, '89). In some species, maternal body reserves further control reproduction during gestation through abortion (Gunn and Doney, '75; Gosling, '86; Forbes, '97) or offspring dumping (e.g. marsupials) under unfavorable foraging conditions (Tyndale-Biscoe and Renfree, '87). This influence of body reserves on reproduction has been documented in different taxa. In several bird species, early maternal body

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*Correspondence to: Catherine Louise Michel, CEBC CNRS, UPR 1934, Villiers en Bois 79360 Beauvoir sur Niort, France.

E-mail: catherine.louise.michel@gmail.com

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condition positively influences both clutch and egg size (Houston et al., 2009); in reptiles, there is a positive relationship between female body condition and reproductive output (Bonnet et al., 2001; Reading, 2004; Litzgus et al., 2008). The general picture that can be derived from these studies is that maternal body reserves positively influence reproduction in vertebrates.

However, the impact of extremely abundant body reserves on fertility and reproductive output remains a poorly explored issue, except for humans. It is important to distinguish the types of maternal body reserves that can be mobilized to fuel reproduction from those that are involved in other roles, such as the isolative fat layers of marine mammals for instance. Disregarding such particular reserves, various body stores (e.g. lipids and amino acids) that can be invested in offspring production are accumulated between reproductive episodes and are consequently exhausted during reproductive expenditure. Consequently, animals navigate between stages of high vs. low body condition, especially in capital breeders (Lourdais et al., 2002). Extreme body reserves can be accumulated when reproduction is abolished and/or when incoming resources greatly exceed metabolic needs. In vertebrates, such extremely abundant (pathologic) body reserves take the form of large lipid deposits in the adipocytes. Obesity refers to the resulting stage where fat body reserves are apparently accumulated to excessive levels. Obesity is not common in wild vertebrates, and data to examine the impact of extremely large body reserves on reproduction do not exist in natural populations. However, obesity concerns an increasing number of people worldwide, along with many domestic animals (mostly pets) and genetically manipulated rodents (German, 2006). Accidental or experimental obesity provides an opportunity to examine the impact of very large fat body reserves on reproduction, and hence to test the notion that body reserves positively influence reproduction in vertebrates.

In obese men, the plasma concentration of testosterone decreases (Kley et al., '80). In women, obesity provokes an earlier menarche, menstruation being initiated when body weight reaches a critical body mass (Frisch and Revelle, '71). Obesity is associated with a lower pregnancy rate in married women and with a higher likelihood of surgery to cure polycystic ovaries (Bray, '97). Different endocrine and metabolic mechanisms are involved in these reproductive consequences: insulin resistance, hyperandrogenism, or elevated leptin levels causing poor reproductive performances (Gambineri et al., 2002; Linne, 2004; Norman et al., 2004). Obesity is associated with higher miscarriage rates (Fedorcsack et al., 2000), for both natural and assisted conceptions (Zaadastra et al., '86; Wang et al., 2000; Loveland et al., 2001). In addition to these negative effects, obesity also influences placenta and neonate morphologies (Abrams and Laros, '86; Kirchengast and Hartmann, '98; Miletic and Stoini, 2005; Frederick et al., 2008). In the other mammals studied to date, i.e. laboratory rodents, obesity did not affect fertility or litter mass, but it can cross generations (Campos et al.,

2008; Shankar et al., 2008). Although it is suspected that excessive fat stores can perturb reproduction in other species (e.g. livestock and pets), the absence of specific studies on this issue precludes generalization. Overall, we still do not have a clear picture of the impact of obesity on reproductive performances in vertebrates.

We studied the effect of obesity on reproductive output in female guinea pigs (*Cavia aperea f. porcellus*). Notably, we assessed the probability of the females to become pregnant, and the influence of early maternal body condition on litter size and offspring characteristics. Guinea pigs easily reproduce in captivity, they tend to store very large amounts of fat (see results), and they have been widely used to better understand human physiology; thus, detailed information on reproduction, including change over time in the utilization of body reserves, is available (Keightley and Fuller, '96; Raffel et al., '96). Reproduction is characterized by a long gestation period, females give birth from one to nine large (80 g) neonates, and the guinea pig is extremely precocial (Trillmich et al., 2007). These features enabled us to focus on the impact of early maternal body reserves on reproductive output (number and size of offspring) without considering the impact of maternal care, and thus simplified experimental design.

MATERIALS AND METHODS

Studied Species

The domestic guinea pig (*Cavia aperea f. porcellus*) is a medium size rodent (≈ 800 g) that reproduces throughout the year and, in contrast to rats and mice, irrespectively to photoperiod as long as sufficient food is provided and ambient conditions do not deviate excessively from thermal neutrality (Trillmich, 2000). In pregnant females, daily food intake is 32.7 ± 3.3 g day⁻¹ on average with mean peak values of 40.8 ± 4.8 g day⁻¹ (Künkele, 2000). In this species, pregnancy entails a massive maternal investment. Most of the offspring development is completed before birth (Künkele, 2000). Maternal body mass increases markedly (e.g. 50% elevation) during gestation and impedes mobility owing to the overload handicap along with prolonged compensating foraging activity. Caviomorphs stand out from other rodents by producing extremely precocial offspring, guinea pigs providing one of the most extreme examples. Compared with altricial species, neonates are physiologically mature (except for reproductive functions), agile, and relatively independent at birth: resembling miniature adults, they have open eyes, exhibit fully developed fur, feeding apparatus, and start to forage almost immediately after birth (Weir, '74).

Body Condition Index, Body Reserves, and Obesity

In animals, body condition is usually expressed as body mass adjusted by size (Hayes and Shonkwiler, 2001). Total body size was measured from dorsal side, as the curvilinear length (in a

straight line, using a flexible ruler) from the tip of snout to the end of the abdomen (putative location of the tail) of the guinea pigs. Body mass was measured using an electronic scale (± 1 g). However, BCI alone provides only relative values that are of little use to estimate fat reserves in living animals. In species where body composition has been investigated, however, it is possible to estimate body reserves of living specimens using allometric relationships between size, mass, and body reserves (Naulleau and Bonnet, '96). Previous studies investigated interindividual variations and changes over time of fat body reserves in both reproductive and nonreproductive guinea pigs (Raffel et al. '96). However, we note that the technique employed (TOBEC), although extremely useful to provide dynamic values (TOBEC is a noninvasive method), can only provide rough estimates and not actual values of the mass of the lipidic reserves deposited in the forms of fat bodies (for further details and discussion, see Hayes and Shonkwiler, 2001). In this study, we euthanized and dissected 34 guinea pigs and weighed the actual mass of the main organs. Specifically, we removed and weighed the fat bodies (particularly well delimited in guinea pigs), liver, digestive tract, gonads, kidneys, skin, lungs, main dorsal muscles, and carcass. Before euthanasia, the individuals were kept in captivity in large outdoor enclosures (15 m \times 5 m) for one year and were fed ad libitum. Although there is no general definition of obesity applicable in all mammalian species, the relationship between the mass of fat bodies relative to body mass provides an accurate index; indeed, adipose tissues tend to develop faster than the other organs when more resources are ingested than can be metabolized, generating abundant fat deposits, especially in humans, but also in guinea pigs (see results), whereas for instance muscle mass does not increase at the same rate. Therefore, we considered that a rapid acceleration of fat body mass relative to the other organs with increasing body mass would indicate a trend toward obesity. We used the allometric relationship between fat body mass against body mass to estimate body reserves in living guinea pigs.

Experimental Design

Thirty-nine adult female guinea pigs (experimental females) were involved in the experiments. Individuals originated from a colony maintained at the Centre d'Etude Biologique de Chizé (France). Using natural color markings, each individual was easily identified. Water and commercial guinea pig food were available ad libitum and the diet was supplemented regularly with fruits and hay. Experimental females had previously successfully produced one or two litters, but none of them had recently reproduced at the onset of the experiment: at least 100 days elapsed between the last parturition and the beginning of the experiment.

We placed each female with an adult male (randomly selected among 20 males) in a cage for 10 days, and then with another male for the same period. We expected that most (i.e. >70%) of

the females would become pregnant; another proportion of the females would not reproduce for various uncontrolled factors as observed in close experimental design (Trillmich, 2000).

Each of the 40 females was kept in an individual box (60 cm \times 50 cm \times 35 cm) with a wood shelter (20 cm \times 15 cm \times 15 cm) and wood shaving as substratum, and a drinking bowl connected to an automatic system provided clear fresh water. Food (Commercial pellets, Moissons du Clos, France) was provided ad libitum. Each female was examined for reproductive and general status and was weighed once a week. Body size and body mass were recorded as described above.

The date of parturition was recorded. As the boxes were examined every day and because births occurred early morning, the maximum deviation from the precise timing of parturition was 12 hr. Number, sex and morphological characteristics (mass, size, color pattern) of the pups were recorded as soon as parturition was observed.

Analyses

Statistical analyses were performed using R7.1. (R-Development Core Team, 2008). Potential deviations from the assumptions of the models were checked using graphical diagnostic tools (Faraway, 2006). BCI was calculated as the residuals from the regression between body mass against body size ($r = 0.58$, $F_{1,88} = 45.48$, $P < 0.01$; using all females involved in the study). Importantly, we used early body condition values (initial body condition) at the onset of reproduction in order to not incorporate into the calculation the mass of the developing embryos (and hence, to avoid circular analyses by placing the mass of the embryos in the two sides of the equation). Three weeks elapsed between the first and last parturition (see results), and such delay complicates the determination of the initial body condition. However, such source of variation was taken into account. Indeed, adult female body size did not vary significantly during the course of the experiment (thus, body size was considered as constant) and each female was weighed on a weekly basis. Therefore, body condition at the beginning of pregnancy was calculated using the body mass recorded during the first estimated week of pregnancy: 7 weeks before the observed date for parturition (the average reproduction duration is 68 days, with the 2–3 weeks corresponding to fertilization, nidation, and very early development being negligible in terms of embryonic mass). Overall, our maximal potential error to calculate initial body condition was approximately 1 week and likely less on average. Importantly, such possible error was equally distributed between the different groups of females examined (see results). The relationship between maternal initial body condition and reproductive output was assessed using generalized linear mixed models with maternal identity as a random factor. To analyze the effect of body mass (continuous variable) and sex ratio (discontinuous variable), we used a logistic regression. In practice, using maternal body mass or maternal body condition

often produced similar trends in the results owing to the strong correlation between these two variables. Interaction terms were all nonsignificant unless otherwise reported.

RESULTS

Body Condition Index, Body Reserves, and Obesity

The fat bodies (main adipose tissues) we removed from the guinea pigs were white, with almost no evidence of blood vessels, and were covered by very thin conjunctive layers, suggesting that fat bodies were essentially made of lipids. Dissections revealed that the mass of the fat bodies increased rapidly after a body mass threshold of approximately 700 g (Fig. 1). Fat stores correlated positively with body condition ($r = 0.77$, $P < 0.01$, $N = 16$), which was particularly apparent when the analysis was limited to the subset of females above the threshold ($r = 0.84$, $P < 0.01$, $N = 9$). Clearly, when fed ad libitum, captive female guinea pigs with limited physical exercise tend to store large amounts of fat tissues. On average, adipose tissue represented 55 ± 34 g ($7.6 \pm 6.1\%$ of total body mass) in the nine autopsied females heavier than 700 g. The mass of the other organs increased linearly with body mass (Fig. 2 for an illustration of dorsal muscles).

We estimated the adipose tissue mass of the 39 experimental females using the equation linking fat mass and body condition obtained on the dissected individuals. The estimated average adipose tissue mass was 107 ± 49 g ($10.4 \pm 3.2\%$ of total body mass). This elevated value was explained by the fact that the 39 experimental females exhibited very high body condition at the beginning of the study, even compared with the relatively fat dissected individuals (ANCOVA with the two categories of guinea

pigs [dissected vs. living] as a factor, body mass as the dependent variable, and body size as a covariate: $F_{1,53} = 5.244$, $P = 0.026$).

Initial Body Condition and Reproductive Status

Among the 39 experimental females, 24 became pregnant and 15 did not. Three weeks elapsed between the first and last parturitions. Pregnant females exhibited a lower initial body condition (-34.1 ± 86.9 , mean \pm SD, range -173.8 – 142.0) compared with nonpregnant females (54.59 ± 164.69 , range -114.62 – 335.17 ; ANOVA with reproductive status as a factor, body mass as the dependent variable, and body size as a covariate: $F_{1,36} = 4.738$, $P < 0.036$; Fig. 3).

In pregnant females, body mass was positively influenced by body size ($F_{1,22} = 16.96$, $r^2 = 0.435$; $P < 0.001$), whereas this relationship was not found in nonpregnant females ($F_{1,14} = 3.411$, $r^2 = 0.208$, $P = 0.087$), suggesting an independent increase of mass relative to body length in the heavier (fattest) females.

Initial Body Condition and Reproductive Output

The proportion of stillborns was low (4 stillborns vs. 88 healthy offspring), mean litter size was 3.7 ± 1.1 (range 1–6), mean litter mass was 322.69 ± 112.2 g (range 112.2–472.5 g) and the sex ratio (males per total) was equilibrated 1.2 ± 0.3 . There was a negative correlation between litter size and initial body condition ($F_{1,22} = 10.19$, $r = -0.56$, $P = 0.004$), similarly using maternal mass as the independent variable ($F_{1,22} = 14.37$, $r = -0.63$, $P = 0.001$). Initial body condition negatively influenced litter mass ($F_{1,22} = 7.67$, $r = -0.510$, $P = 0.011$; using maternal mass: $F_{1,22} = 11.68$, $r^2 = -0.59$, $P = 0.002$). Initial body condition had no effect on sex ratio ($\chi_{1,22} = 0.098$, $P = 0.754$).

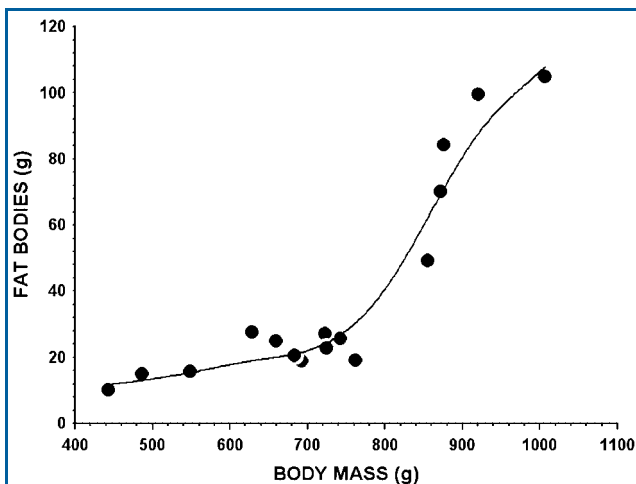


Figure 1. Relationship between the mass of the fat bodies (g) and body mass in female guinea pigs. A polynomial relationship ($r = 0.95$) provided a better fitting compared with a linear relationship ($r = 0.85$), suggesting a threshold effect.

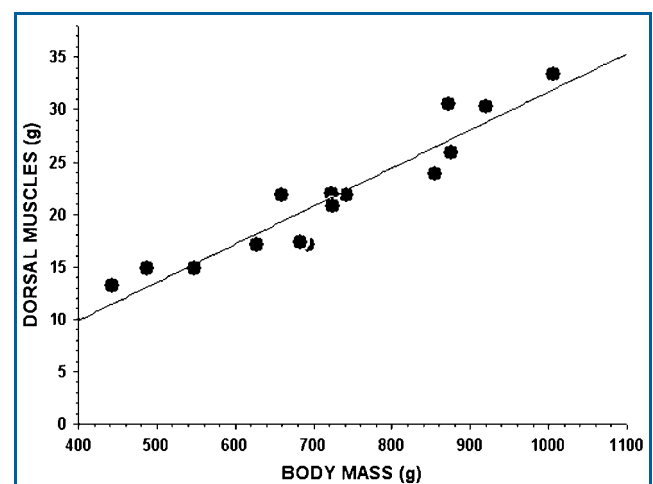


Figure 2. Relationship between the mass of the dorsal muscles (g) and body mass in female guinea pigs. A linear relationship provided a better fitting (0.94) compared with a polynomial relationship (0.85).

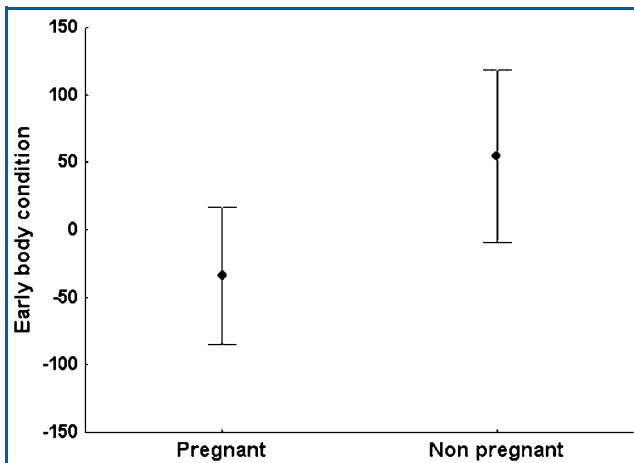


Figure 3. Relationship between early maternal body condition (an index of fat stores) and future reproductive status. Means are presented with their 95% confidence interval.

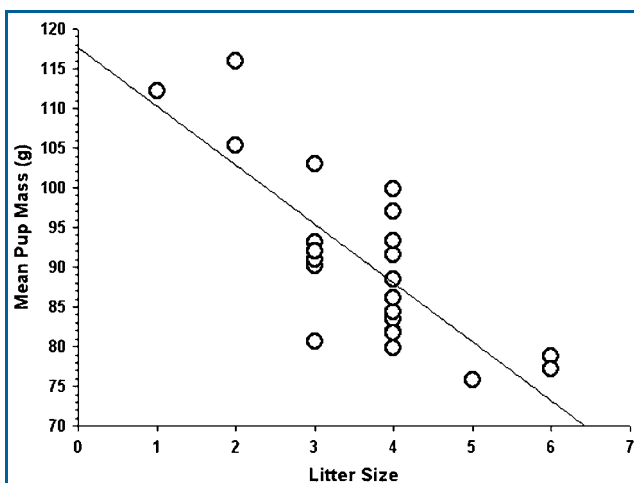


Figure 4. Relationship between mean offspring mass and offspring number in guinea pigs.

Initial maternal body condition positively influenced mean pup mass ($F_{1,22} = 8.73$, $r = 0.53$, $P = 0.007$; using maternal mass: $F_{1,22} = 10.15$, $r = 0.56$, $P = 0.004$). When litter size increased, the mean body mass of the pups decreased ($F_{1,22} = 34.33$, $r = -0.78$, $P < 0.0001$; Fig. 4). Stepwise regressions, including early maternal mass (or early maternal body condition), did not improve this analysis.

Maternal Changes in Body Mass and Reproductive Output

Pregnant females gained weight during gestation, and this change (i.e. the difference between postpartum body mass minus initial body mass) was correlated with litter size ($F_{1,22} = 4.28$, $r^2 = 0.163$, $P = 0.050$) and mass ($F_{1,22} = 4.394$, $r^2 = 0.166$,

$P = 0.048$). We expected that those females exhibiting greater reproductive investment (e.g. larger litters) would be more emaciated at parturition caused by a greater demand; however, we found no effect of litter size or mass on the maternal postparturition mass (respectively, $F_{1,22} = 0.031$, $r^2 = 0.001$, $P = 0.864$; $F_{1,22} = 0.075$, $r^2 = 0.003$, $P = 0.786$).

DISCUSSION

Several results suggest that the 39 experimental female guinea pigs involved in our study tended to be obese. First, in the dissected individuals, fat body deposits were particularly well developed (on average, 7% of the total body mass and on average adipose stores represent 2% of the total body mass in rats; Enzi et al., '86); however, the 39 experimental females were significantly heavier with estimated fat body deposits representing 10% of the total body mass on average. This value does not represent total body lipid mass which incorporates the lipids constitutive of all other tissues, and hence underestimates the actual total body lipid mass. Second, in captivity, female guinea pigs fed ad libitum tend to rapidly store lipids in the fat bodies above a body mass of 700 g (Fig. 1) and all the 39 experimental females weighed more than 750 g. Third, further analyses performed in the dissected females revealed that above the 700 g body mass threshold (Fig. 1), adult guinea pigs tended to store fat tissues more rapidly compared with all the other tissues (none of the other organs weighed exhibited this rapid increase), as observed in different mammal species, including humans. Such predisposal to store very large amounts of fat relative to other tissues is an important prerequisite to exhibit a trend toward obesity.

Various techniques have been employed to quantify fat reserves in mammals. In humans, the body mass index (BMI) (kilograms/meters²) is well correlated with both the percentage of adipose tissues and with total amounts of body lipids. People with a BMI exceeding 25–30 are considered as obese. In animals, body condition scoring (BCS) has been used, notably in dairy cows, beef cows, goats, sheep, horses, mice, and rats. The BCS ranges from 1 to 5, depending upon muscle mass and fat stores, prominence of skeletal structure (vertebral column), and bony protuberances, but precise values of body composition are lacking precluding broad comparisons across species. In rats, a Lee index, calculated as the cube root against the ratio of body mass (g)/snout–anal length (mm), has been validated (Bernardis and Patterson, '). Below a value of 0.3, individuals are considered as normal and obese above. In our 39 experimental guinea pigs (rats and guinea pigs exhibit relatively similar morphologies), the Lee index (highly correlated to other condition indexes) was systematically above 0.3. Overall, we conclude that the 39 experimental females involved in the study exhibited elevated absolute body condition, and all had large body reserves, notably well-developed fat bodies. We acknowledge, however, that we cannot state that our guinea pigs were in a pathologic stage, as

observed in extremely obese persons that exhibit markedly reduced mobility, for instance. This also means that the negative impact of fatness on reproductive performances we documented might well be more pronounced in extremely obese guinea pigs.

In this study, female reproductive performances were negatively affected by initial body condition. High initial body condition decreased the probability to become pregnant ($\chi^2_{1,37} = 4.572$, $P = 0.032$), and in addition reproductive output (mass and number of offspring in a litter) were lower in the fattest females. The few studies available on this topic provided contrasting results. In rats, obesity does not affect reproductive capacity (Campos et al., 2008; Shankar et al., 2008), while in humans a marked negative impact has been recorded (Bernardis and Patterson, '68). Interestingly, similar to humans (but in contrast to normal rats, for instance), sedentary guinea pigs with unlimited access to food tend to store very large amounts of fat deposits (this trend might be stronger due to the provision of very rich food), probably more than what they can mobilize during reproduction, especially when food is provided during vitellogenesis, gestation, and lactation (note that postnatal parental care and lactation are limited in guinea pigs, notably compared with other same-size mammals). In women, the negative impact of obesity on reproductive performance has been attributed to various perturbations of the endocrine and metabolic mechanisms; notably, through insulin resistance, hyperandrogenism, or elevated leptin levels (Gambineri et al., 2002; Linne, 2004; Norman et al., 2004). It would be informative to explore similar issues in the obese guinea pigs. Indeed, these rodents exhibit numerous physiological similarities with humans (Keightley and Fuller, '96).

Obese women tend to have heavier infants (Abrams and Laros, '86; Kirchengast and Hartmann, '98; Frederick et al., 2008; Miletic and Stoini, 2005). In rats, obesity did not affect litter mass or size (Campos et al., 2008; Shankar et al., 2008). However, in our study, the fattest female guinea pigs produced heavier offspring (Fig. 4), although this effect was a mere consequence of the strong trade-off between offspring number and size (Smith and Fretwell, '74) documented in many species, notably in guinea pigs (Gajewska, '65; Kasparian et al., 2005 for the cavy; Stern and Bronner, '70; Stern, '71). We cannot speculate on the physiological mechanisms underlying the divergences between species, but our results suggest that studying guinea pigs might be useful to better understand possible negative impact of excessive fat stores on mammalian reproduction.

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