

## Relationship between menarche and fertility in long-tailed macaques (*Macaca fascicularis*)

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**Abstract.** We attempted to elucidate female reproduction in long-tailed macaques (*Macaca fascicularis*). These monkeys have a non-seasonal menstruation cycle, which makes them suitable subjects for studies in a variety of fields including medical science and regenerative medicine. We analyzed individual breeding data including time of menarche, start of regular menstruation, and first pregnancy. These three events are related to the maturation of female long-tailed macaques. All research subjects were female long-tailed macaques bred at the Tsukuba Primate Research Center. The study comprised 45 females; we included time of menstruation, male-female cohabitation, and first pregnancy in their growth records. We extracted age and weight data relating to menarche, start of regular menstruation, and first pregnancy from these records. In the two years typically required from menarche to first pregnancy, the body weight increased by approximately 500 g (21% of the weight at menarche); it is clear that there is a significant physical change after menarche. Our findings suggest that female monkeys are not necessarily mature enough for pregnancy at menarche. Therefore, the use of the word “maturity” in terms of fecundity may be more accurate after the start of regular menstruation. This is what we term “adolescence” in the developmental process. Therefore, *M. fascicularis* monkeys are candidates for an animal model of human adolescence.

**Key words:** Female fertility, Female reproduction, Long-tailed Macaque, Menarche

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Monkeys are essential study subjects for the rapid progression of medical science and regenerative medicine. Their anatomies, physiologies, and particularly their reproductive processes are similar to those of humans [1–3]. Monkeys also have a menstrual cycle and menarche. Of the more than 200 monkey species, macaques in particular are used because there has been a significant accumulation of their basic data [4]. Researchers have frequently reported the reproductive physiology of rhesus and long-tailed macaques; the menstruation cycle of rhesus macaques is 25.5–29.5 days [5], and that of long-tailed macaques is  $29 \pm 4$  days [6]. Although the two species have similar menstruation cycles, rhesus macaques have a breeding season and long-tailed macaques breed throughout the year [7]. To achieve a better understanding of their differences and similarities, it is important to continue using these monkeys as study subjects. The Tsukuba Primate Research Center at the National Institute of Biomedical Innovation, Health, and Nutrition (TPRC) has a breeding/maturing colony of long-tailed macaques. In the present study, we analyzed data to clarify the relationship between menarche and fertility in long-tailed macaques.

Sometimes, menarche indicates that a female is fully mature. By

the time of the first menstruation, the development of a female's genitals/reproductive organs and endocrine system is considered complete. From this perspective, menarche has been considered the indicator of maturity. However, the stabilization of the menstrual cycle after menarche takes time. Therefore, we hypothesize that although menarche suggests that a female has achieved a certain degree of physical development in terms of her reproductive organs and endocrine system, it does not necessarily indicate that she is fully mature.

The empirical data on sexual maturation in monkeys indicate that rhesus monkeys undergo endocrine changes based on their menstruation cycle [8]. Their average age at menarche is 29.8 months (ranging from 20 to 42 months) [9], and their menstrual cycles commence at 28–32 months of age [10]. However, there is little information about the age of long-tailed macaques at menarche or commencement of menstruation.

In the present study, we created a male-female cohabitation environment when a female showed signs of ovulation, and investigated the pair's reproductive performance. This male-female cohabitation arrangement was based on the following study. When the levels of serum follicle stimulation hormone (FSH) in long-tailed macaques were monitored, the results suggested that in 60% of the animals, FSH increased 10–11 days after menstruation, and ovulation was observed 1–2 days later. Therefore, the optimal cohabitation time was judged to be approximately 12 days after menstruation. Consequently, we initiated male-female cohabitation 11 days after menstruation, and allowed cohabitation to continue for 3–7 days [11].

Monkeys display a high level of cerebral activity; with regard

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to reproduction, physical growth is a matter of course, but brain development cannot be ignored. The sexual behavior of immature primates is similar to that of mature animals [4, 12, 13]. Based on these earlier findings, it is thought that sexual/reproductive behavior is associated with social relationships. Whether the data for fully mature individuals are also applicable to immature individuals is debatable. In the present study, we analyzed and discussed the clear numerical reproductive data pertaining to a set of *M. fascicularis* females, taking into account psychological and sociological factors.

Some authors have asserted that body weight determines the start of puberty [14–17]. We propose that the simplest and most reliable means of evaluating the growth of long-tailed macaques is to monitor the variation in their body weight. Jayo *et al.* divided their animal subjects into the following age ranges: young (3.7–6.4 years), adult (6.5–10.5 years), and mature (10.5–22.0 years); their results revealed weight gain and changes to bone density [18]. In this manner, many researchers have used weight as an index for body development; however, an analysis of female menarche and the maturation process has not been carried out in long-tailed macaques. Around the time of menarche, female monkeys experience significant changes to their bodies. We assumed that females mature psychologically and physically from the time of menarche to pregnancy, and that the integrity of the reproductive system is retained during growth.

In rhesus monkeys, age and weight are related to puberty [19]. In the present study, we focused on age and weight at the time of menarche, the start of regular menstruation, and the first pregnancy.

First, we focused on the age at menarche of the long-tailed macaques, because very little research has been carried out in this regard to date. We then determined the time between the start of menarche to the beginning of regular menstruation and first pregnancy.

## Materials and Methods

### Animals

The subjects comprised 45 adult female long-tailed macaques (*Macaca fascicularis*) that were born in the TPRC breeding colony. Each monkey was housed in a separate cage (0.5 m wide × 0.8 m high × 0.9 m deep; stainless steel mesh). Each cage was structured so that it could be easily connected to the cages on either side. The air in the breeding room was replaced 12 times each hour, and was maintained at approximately 25 ± 3°C and approximately 60% humidity (when the room was being cleaned, the humidity increased temporarily). The room was lighted for 12 h per day from 0700 h to 1900 h, and the monkeys were provided with fruit (100 g) and monkey chow (70–100 g). All subjects were fed the same amount each day. Water was made available *ad libitum*.

Experienced animal technicians inspected the monkeys daily for signs of menstruation or abnormalities. The health, appetite, bowel activity, and menstruation of the monkeys were monitored by animal technicians. The collected data were maintained on a computer. If an abnormality was found in a monkey (e.g., in terms of health, appetite, fecal condition and/or menstruation), the monkey was examined and treated by a veterinarian.

At the TPRC, the infant-rearing program is designed so that each monkey develops normally. After weaning at 5–6 months, the infants are placed in a peer group program until they are 2 years old, and are

reared with two to four other animals. Some newborns are separated from mothers with inadequate raising skills and fostered by humans. However, they still participate in the same peer group program as the other infants [20].

### Menstruation/pregnancy confirmation

Menstruation is a physiological phenomenon in which the thickened endometrium is discharged from the body. Estrogen and progesterone—which are steroid sex hormones secreted by the ovaries in response to stimulation by FSH and luteinizing hormone (LH)—cause the endometrium to thicken in preparation for implantation. The endometrium is discharged if implantation does not occur. In the present study, we interpreted the results on the premise that menstruation is proof that the endometrium hypertrophy and shedding that accompany these hormonal dynamics are occurring normally.

Any hemorrhage caused by menstruation was observed as blood marks under the cage. To ensure the animals remained healthy, each monkey received a medical examination (including blood tests, etc.) from a veterinarian every 2 years. When the animals were anesthetized for medical examination, or for transfer between rooms for cohabitation, their weights were measured and the data entered into a computer [20].

Pregnancy was confirmed by ultrasonography, which was conducted at 3 weeks and 5 weeks after the start of cohabitation. It was possible to detect a successful pregnancy by the third week. At 5 weeks of pregnancy, a fetal heart signal could be accurately and clearly detected. For a pregnancy diagnosis, the monkeys received an intramuscular injection of 1–5 mg/kg ketamine hydrochloride. Echo jelly was then applied, and the uterine cavity was examined using an ultrasonic probe. If a female was pregnant, a dim shadow was discernable in the ultrasonic image due to the fetal sac in the uterine cavity. However, if a female was not pregnant, there was a horizontal line in the center of the ultrasonic image.

### Male-female cohabitation environment

As often as possible, we created a male-female cohabitation environment when we observed menstruation. In rare cases, we were unable to prepare an appropriate environment, and cohabitation was impossible because of the lack of an appropriate male or female living environment. The subjects participated in 378 cohabitations (771 menstrual periods observed). Male-female cohabitation was initiated on the eleventh day following menstruation. The animals were anesthetized before transfer, and cohabitation was facilitated using adjacent cages that could be connected together.

The study was approved by the Ethics Committee of the National Institute of Biomedical Innovation (NIBI), and the experiments were conducted in accordance with NIBI guidelines.

### Data analysis

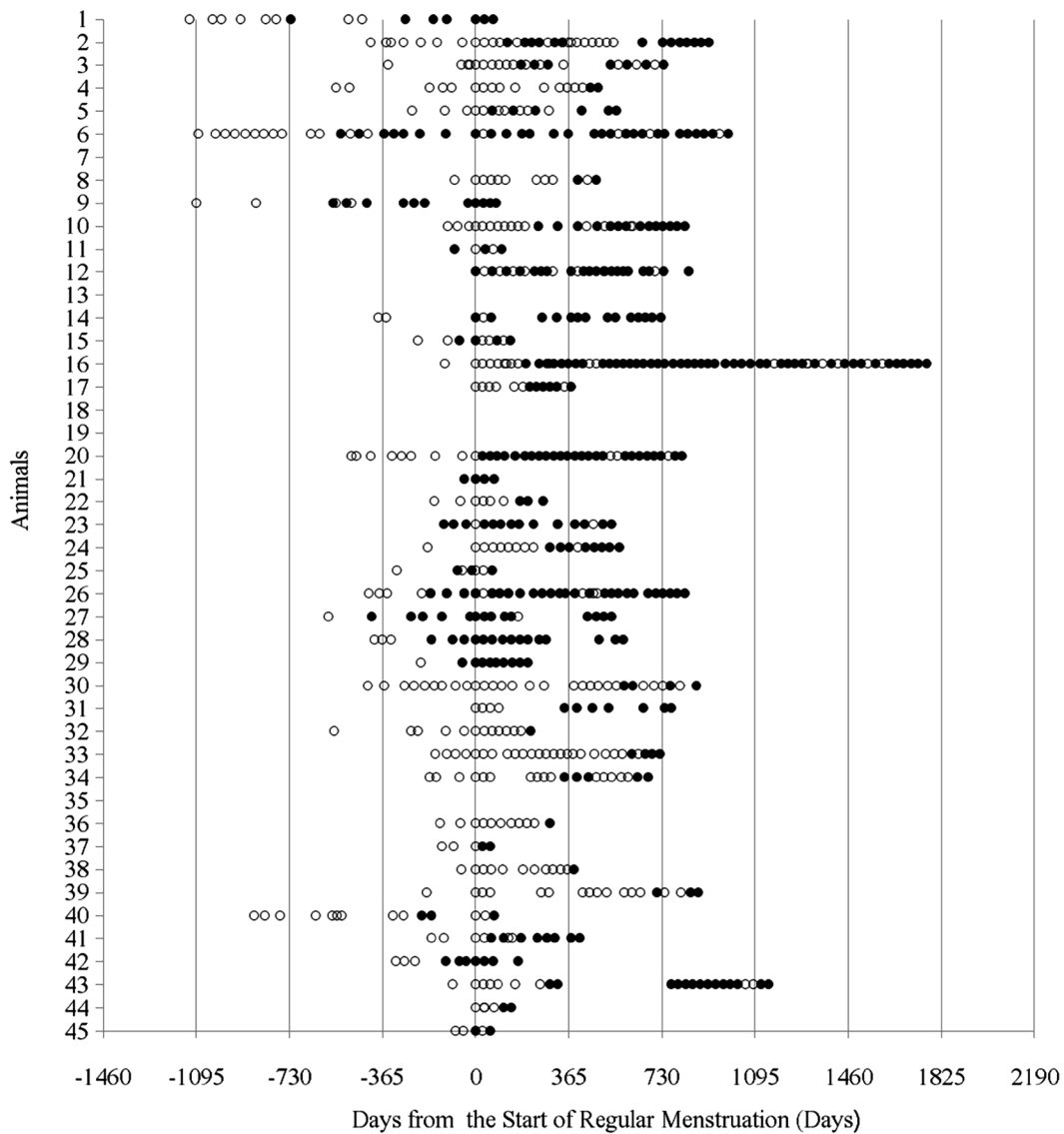
We investigated the reproductive process in the female macaques over three periods: the first detection of menses (menarche), the start of regular menstruation, and first pregnancy. We selected subjects born between 2002 and 2009 that become pregnant before November 2014. Table 1 lists definitions of the terms used in our analysis.

Figure 1 shows the data for the 45 females from first menstruation to first pregnancy. The figure indicates the menstruation data,

**Table 1.** Definition of terms

Periods		Definitions
First menstruation (Menarche)	Age in days	The first day of menstrual flow was Day 1 of the menstrual cycle; the day was defined in days of age at first menses.
	Weight *	We used the weight recorded closest to the time of first menses.
The start of regular menstruation	Age in days	We defined the start of regular menstruation to be when menses in a 25–35 day menstrual cycle was observed twice.
	Weight*	We used the weight recorded closest to the start of regular menstruation.
First pregnancy	Age in days	We defined age in days from birth to the first day of the last mating in this study (presumed to the last mating day = ovulation time = fertilization day).
	Weight *	We used the weight recorded closest to the time the female became pregnant for the first time.

\* If the weight measured for the targeted data was within three months, we used the closest weight measurement. However, if the animal's weight had not been measured within three months for the target data, we used the average weight measurement for the target data before and after.



**Fig. 1.** The process of sexual maturity in 45 animals. The horizontal line shows the days from the first detection of menses (menarche); the vertical line at 0 indicates the start of regular menstruation. The open circles represent menstruation and the closed circles represent the number of cohabitations subsequent to menstruation. Each animal's first open circle represents menarche, and the last filled circle represents first pregnancy. Animals 7, 13, 18, 19, and 35 were not observed from the start of regular menstruation because they became pregnant before they began to menstruate regularly.

**Table 2.** Age at first menstruation, at the start of regular menstruation, and at first pregnancy

	Average age (Days)	Standard deviation	Minimum	Maximum	Quartile		
					25	Median	75
First menstruation	1,195.1	208.7	801.0	1,568.0	1,075.7	1,179.0	1,291.5
Start of regular menstruation	1,490.1	333.2	985.0	2,675.0	1,318.0	1,428.5	1,562.8
First pregnancy	1,987.0	447.0	1,421.0	3,233.0	1,607.0	1,978.5	2,220.3

**Table 3.** Weight at first menstruation, at the start of regular menstruation, and at first pregnancy

	Average weight (kg)	Standard deviation	Minimum	Maximum	Quartile		
					25	Median	75
First menstruation	2.38	0.28	1.85	3.04	2.18	2.37	2.52
Start of regular menstruation	2.59	0.38	1.94	3.83	2.37	2.50	2.71
First pregnancy	2.86	0.38	2.34	3.79	2.58	2.75	3.08

including the number of days from first menstruation to the first day that mating took place. Five animals (animals 7, 13, 18, 19, and 35) were not observed from the start of regular menstruation because they became pregnant before they began to menstruate regularly. Statistical processing was carried out on 40 animals, excluding these 5.

First, we demonstrated the indication of maturity by statistical methods based on Bayes' estimation (Markov Chain Monte Carlo method). We calculated the increase in age and weight for each of the three periods. We used the statistical packages available at <http://y-okamoto-psy1949.la.coocan.jp/bayesian/NormalOneVar/> for all analyses.

We used the *t*-test for age and weight. Four animals showed characteristic development but started menstruating regularly immediately after menarche. We used the *t*-test to compare these four animals to the remaining 36 (from a total of 45 animals, excluding the five that became pregnant before regular menstruation).

## Results

In Figure 1, the ordinate axis indicates each animal and the abscissa axis indicates menstrual periods, cohabitation, and the start of regular menstruation. Out of 40 animals, only 4 started menstruating regularly immediately after menarche (10% of the total number of females). Of the 19 females scheduled to copulate before the start of regular menstruation, only 5 became pregnant (26% of the 19 females). In other words, 14 of the 19 females (74%) became pregnant after the start of regular menstruation. Of the 40 animals, the 3 females (animals 32, 36, and 38) that were menstruating regularly became pregnant at first cohabitation (8%).

Table 2 shows the average age at menarche, at the start of regular menstruation, and at first pregnancy. The average age at menarche was 1,195.1 days (approximately 3 years and 4 months). The average ages at the start of regular menstruation and at first pregnancy were 1,490.1 days (approximately 4 years and 1 month) and 1,987.0 days (approximately 5 years and 5 months), respectively. The time from menarche to the start of regular menstruation was 295.0 days (approximately 9 months). We found that 792.0 days (approximately

2 year and 2 months) passed from the start of regular menstruation to first pregnancy.

Table 3 shows the average weight at menarche, at the start of regular menstruation, and at first pregnancy.

The average weight at menarche was 2.38 kg. The average weights at the start of regular menstruation and at first pregnancy were 2.59 kg and 2.86 kg, respectively. The monkeys gained weight after their first menstrual period. From menarche to first pregnancy, the monkeys gained 0.48 kg (a 20% increase from the start of menarche).

We obtained the statistical estimates for the number of days using Bayesian posterior probability distributions. The section from the start of regular menstruation to menarche was MAP 293.40 days (MAP = maximum *a posteriori* probability; 95% confidence interval (95%CI): 188.95–401.97). The section of pregnancy to the start of regular menstruation was MAP 494.77 days (95%CI: 355.08–639.95), and the section of pregnancy to menarche was MAP 789.32 days (95%CI: 618.73–966.63).

We obtained the statistical estimates for weight using Bayesian posterior probability distributions. The section from the start of regular menstruation to menarche was MAP 0.21 kg (95%CI: 0.08–0.34). The section of pregnancy to the start of regular menstruation was MAP 0.27 kg (95%CI: 0.17–0.38), and the section of pregnancy to menarche was MAP 0.48 kg (95%CI: 0.36–0.60).

In a comparison between the four females that started menstruating regularly immediately after menarche and the remaining 36 females, the difference between the four females' ages at menarche (average 1,382 days) and the remaining 36 females' ages at menarche (1,140 days) was statistically significant ( $P = 0.032$ ). The *t*-test calculation for the other periods (regular menstruation and first pregnancy) revealed that the differences were not statistically significant at the  $P = 0.05$  level. Regarding the four females' weights, the average weight at menarche (uniform regular menstruation) and first pregnancy were 2.47 and 2.74 kg, respectively. However, the remaining 36 females' weights at menarche, regular menstruation, and first pregnancy were 2.32, 2.58, and 2.88 kg, respectively. Calculations using the *t*-test showed that these differences were not statistically significant at the  $P = 0.05$  level.

## Discussion

In the present study, we investigated female monkeys from the first detection of menses (menarche), through the start of regular menstruation, to first pregnancy. These three periods are associated with female reproductive maturity in long-tailed macaques. The data regarding the animals' date of birth, menarche, and regular menstruation were exact, and our analysis was based on numbers of days. It is often difficult to analyze time-series data in monkeys, but this was possible in our breeding colony.

There is a paucity of data on menarche in long-tailed macaques. On average, menarche begins at 1,195.1 days (approximately 39.8 months) of age, and the average body weight at that time is 2.38 kg. The earliest reported menarche was 801 days, at which time the body weight was 1.85 kg. Age (in days) and weight are important regarding menarche in long-tailed macaques; we consider that those two conditions are required for menarche. The average age at menarche of rhesus monkeys—which belong to the same genus as long-tailed macaques (*Macaca*)—is 29.8 months [9], which differs from that of long-tailed macaques. However, because the weight of rhesus monkeys at the time of menarche is unknown, it was impossible for us to compare data between the two species of monkey. Moreover, long-tailed macaques breed year-round, whereas rhesus monkeys have a breeding season, so their breeding systems are profoundly different. We believe further research on their differences and characteristics is warranted.

In the present study, we attempted to prove that menarche does not necessarily presage the immediate onset of regular menstruation. On average, the monkeys were 1,490.1 days old when they commenced regular menstruation, and their average weight at that time was 2.59 kg. Using Bayesian analysis, we estimated that an average of 293.4 days passed between menarche and the start of regular menstruation, and the weight of the monkeys increased by 0.21 kg during that time. Obviously these results suggest that monkeys continue to grow after menarche, which may mean their subsequent reproductive status continues to improve. Furthermore, only 10% of the monkeys achieved regular menstruation immediately after menarche. The remaining 90% required a term of growth before the start of regular menstruation. We think that this specific period in the monkeys' maturation process is important.

We supposed that the start of regular menstruation signaled the ability to reproduce; however, we found that the average age of first pregnancy was 1,987.0 days, and the average weight was 2.86 kg. Bayesian analysis allowed us to estimate that 494.8 days passed between the beginning of regular menstruation and first pregnancy, during which time the weight of the monkeys increased by an average of 0.27 kg. Menarche alone did not support pregnancy; therefore, the monkeys could not be considered completely mature at menarche. Bercovich and Goy (1990) reported that menstrual bleeding can occur without ovulation, and concluded that menarche and ovulation should be considered separately [9]. The possibility has been raised that menarche does not necessarily equate to ovulation, which is a prerequisite of pregnancy. Even in monkeys with regular menstruation, all the requisite conditions for pregnancy may still not be present. We considered the minimum physical requirements for pregnancy to be 1,421.0 days of age and a weight of 2.34 kg. The

onset of reproductive function can be regulated by both exogenous (photoperiod) and endogenous (fat storage) cues. The fat store can be predicted by weight [21]. Our daily records confirmed female body changes, such as fat accumulation at 5 years of age. From 3 years of age (menarche) to 4 years (the start of regular menstruation), the monkeys' various reproductive organs matured; over the subsequent year, the monkeys stored fat, presumably as a result of hormonal influence, to become fully mature. Considering that the continuation of bodily changes and the average age of first pregnancy both tended to occur at approximately 5 years, fat accumulation could be related to first pregnancy. However, we could not determine whether fat accumulation contributes to pregnancy or the endocrine system enables pregnancy by creating factors that promote fat accumulation. In any case, the physiological progression from pregnancy to parturition requires a considerable energy input. Because fat accumulation takes place in the same phase as first pregnancy, it is considered very important for growth.

In the present study, four animals began regular menstruation immediately after menarche. Their menarche (average 1,382 days) was later than the average. This suggests that when those four monkeys achieved menarche, their physical condition was sufficient to support regular menstruation. Therefore, there was no delay in reaching sexual maturity in the four animals. Furthermore, the period from menarche to first pregnancy was shorter than that experienced by many of the other animals. However, the weight at pregnancy of the four monkeys was equivalent to that of the other animals. This may indicate that achieving a certain weight after menarche is more relevant to fertility than the period after menarche. Five animals were excluded from the analysis because we could not ascertain the exact start of their regular menstruation. It was possible to estimate that their average weight at first pregnancy (2.66 kg) was the same as that at the early stages of regular menstruation. In the present study, we determined regular menstruation to be marked by three menstrual periods after menarche. By this definition, we had no other choice but to exclude some data. An endocrine analysis is indispensable for elucidating the function of regular menstruation, and this will become an increasingly important issue in the future.

We found that more than 2 years (789.3 days) was required for the monkeys to pass from menarche to first pregnancy. During this period, body weight also typically increased by approximately 0.5 kg. The body weight of the monkeys increased by 21% of their weight at menarche, so it is clear that they experienced a significant bodily change after the first detection of menses. In primates such as cynomolgus monkeys, which have a menstrual cycle, menarche may be one of the indications of physiological sexual maturity. However, the results of our study suggest that menarche does not necessarily indicate that the animal is sufficiently mature to become pregnant. Furthermore, some researchers have suggested that infant mortality increases in both animals and humans when the mothers are too young for pregnancy [22, 23]. When a female reaches maturity, the development of her ovaries and uterus should be complete, and her brain should be capable of releasing gonadotropins, i.e., LH and FSH. Moreover, when positive/negative feedback is functioning in the endocrine system, the female begins regular menstruation. When a female starts regular menstruation, she is considered to be completely sexually mature.



However, in our study only 8% of regularly menstruating females became pregnant at first cohabitation (3 of 40); the remaining 92% became pregnant after copulating multiple times. In short, the majority of the females had to copulate more than once to become pregnant. These results suggest that complete development of the sexual organs is not the only factor necessary for pregnancy. Even infant long-tailed macaques display “mounting” sexual behavior [24]. Furuichi, Connor and Hashimoto [25] described three types of sexual behavior in immature bonobos: sexual behavior during play; copulation-like sexual behavior; and use of sexual behavior to control social relationships. Such experimentation and social learning may affect the maturity of monkeys with regard to pregnancy, and our results indicate the necessity of a certain period to interpret the psychological, ethological, and sociological factors in a breeding environment in which physical contact is restricted. This was what we termed “adolescence” in the developmental process. Therefore, the monkeys are potential animal models of human adolescence.

It is clear that the start of menarche and the start of regular menstruation do not necessarily indicate conditions for pregnancy. Complete sexual maturity in terms of fertility may occur much later than the start of regular menstruation in female long-tailed macaques. However, we did not clarify the relationship between pregnancy and fat storage in the present study; we intend to investigate this relationship in the future.

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