

THE CONDITION OF THE REPRODUCTIVE SYSTEM OF THE MATURE FEMALES OFFSPRING BORN TO MOTHERS WITH PLACENTAL INSUFFICIENCY*

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Nowadays, female reproductive system suffers from different factors that influence on its condition. It is well known, that egg cells of future woman start forming in her mother's uterine and continue developing up to the moment when mature egg cell merges with sperm cell forming zygote. This prolonged process continues several years and depends on large number of different factors. The first crucial period of female reproductive system developing is the embryonic period. It is very important for future woman health how this period will come about, because long-term consequences of some factors impacting during pregnancy may manifest itself decades later after birth and their effects may be severe and hardly predicted [1–3].

The condition of pregnancy is characterized by the different internal and external factors such as body and reproductive woman health, age at the pregnancy moment, the duration of the negative factors impact, uncontrolled consuming of drugs, alcohol, and cigarettes and so on [4–6].

The connection between mother's organism and fetus during pregnancy depends on placenta condition [7]. The fetoplacental complex is the functional system which provides essential conditions for fetal developing [8]. The disturbances of gas exchanging processes and nutrients transport, the hormonal function of the fetoplacental complex [9] and other disorders on the placenta pathological conditions lead to fetus uterine hypoxia, delaying of its growing

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and developing and to adverse consequences in the perinatal period [10 – 12]. These changes of the system «Mother-Placenta-Fetus» may cause the disturbances of placenta and fetus functioning and, finally, to the fetoplacental insufficiency (FPI) developing. Actually, placenta takes the important role in optimal developing and functioning of the fetus. The structure and functions of this temporary organ may adapt to the different external stressors. In case of failed adaptation or inadequate placenta maturing the birth of healthy child is under threat

and may cause a developing of adult's diseases in future.

These days, the number of reproductive-aged women giving birth at later age is growing. According to the literature data, this fact influences on the fertilization, pregnancy, delivery, developing and functioning of child.

Therefore, the purpose of this investigation was the studying of the influence of FPI long-term consequences on the reproductive system functioning of mature female offspring born to different-aged mothers.

MATERIALS AND METHODS

The experimental animals have been kept in the standard conditions of vivarium, under natural sources of light, water regime ad libitum and diet recommended for rats. The investigation has been carried out according to the National «General Principles for Animal Research Ethics» (Ukraine, 2001) which corresponds to the «European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes», (Strasburg, 1985) [13], and «Guide for Research Ethic Committee», 2012 [14].

The healthy, mature rat's females-mothers Vistar line, young (3–4 months) and mature (8–10 months) reproductive age with normal four- to five estrus cycle have been used in the investigation. The presence of the sperm cells in the morning vaginal swabs has been considered to be the first day of pregnancy. With the aim to receive the offspring four experimental groups of animals have been formed. Each group contains 7 rats. The first and the second group were performed by intact animals of relevant age. Rat's females with experimental FPI of young and mature reproductive age have been united into third and fourth groups accordingly. The modeling of FPI has been carried out by daily subcutaneous introduction of

50% tetrachloromethane oil solution in dose of 2 ml/kg of body weight to females from 12 to 18 day of pregnancy. After offspring birth the reproductive function of rat's females in the age of 3 months has been researched. The general duration and estrus cycle's phase structure of female offspring have been studied during 16 days that corresponds to three-to-four estrus cycles. All the animals in the age of 130 days of life have been killed by quick decapitation. The reproductive organs, pituitary gland, thymus gland, adrenal glands, kidneys, liver and spleen have been removed and weighed. The number of mature ovarian follicles in each ovary has been calculated. The blood samples stored at temperature -18°C have been collected for determination of estradiol (E_2) and testosterone (T) levels. The sex hormones levels have been determined by test-sets «Estradiol-IFA» and «Testosterone-IFA» (LLC «CHEMA», Kyiv).

The normal distribution of variables has been calculated according to Kolmogorov-Smirnov criterion. Me — median; s — standard deviation; P — statistical significance of variances between the same sex groups according to the Newman-Keuls criterion. The verification of the statistic hypothesis has been carried out at significance level ($p < 0.05$).

RESULTS AND THEIR DISCUSSION

The different E_2 baselines in intact groups of offspring born to mothers of two groups of age have been detected. The E_2 hormone baseline in females born to mothers of mature reproductive age was diminished by 62% than in offspring of young mothers (table 1). The T hormone level and T/ E_2 ratio were without

changes in both groups. Probably, this fact may be explained by decreasing of general sex hormones level in women that have pregnancy in the mature reproductive age which characterized by gradual declining of reproductive function by comparison with young women [15, 16].

Table 1

Concentration indices of sex hormones in 120-days female offspring of intact and tested animals, Me ± s

Group of offspring (n = 7)	Index		
	Estradiol, nmol/l	Testosteron, nmol/l	Ratio T/E ₂ , cond. un.
1. Intact offspring of young mothers	0.70±0.18	0.90±0.25	1.80±1.27
2. Offspring of young mothers with FPI	0.90±0.04 ^a	2.00±0.26 ^a	2.22±0.72
3. Intact offspring of mature mothers	0.20±0.03 ^{a,b}	0.90±0.09	4.50±0.71
4. Offspring of mature mothers with FPI	0.20±0.11 ^{a,b}	2.70±0.64 ^a	7.00±2.89 ^{a, b, c}

Notes:

^a Mismatch probability among indices in group 1 and 2, 3,4; p < 0.05;

^b Mismatch probability among indices in group 2 and 3, 4; p < 0.05;

^c Mismatch probability among indices in group 3 and 4; p < 0.05.

Table 2

Absolute organs masses of female offspring of intact and tested animals, Me ± s

Group of offspring (n = 7)	Liver, g	Pituitary gland, g	Kidneys, g	Adrenal gland, g
1. Intact from young mothers	5.00 ± 0.33	0.007 ± 0.002	0.48 ± 0.07	0.019 ± 0.003
2. Offspring of young mothers with FPI	4.60 ± 0.69	0.007 ± 0.004	0.51 ± 0.07 ^a	0.018 ± 0.002
3. Intact offspring of mature mothers	5.19 ± 0.26 ^c	0.007 ± 0.002	0.45 ± 0.02 ^{b, c}	0.017 ± 0.004 ^c
4. Offspring of mature mothers with FPI	4.32 ± 0.52 ^{a, b}	0.006 ± 0.001	0.41 ± 0.03 ^{a, b}	0.014 ± 0.002 ^{a, b}

Notes:

^a Mismatch probability among indices in group 1 and 2, 3,4; p < 0.05;

^b Mismatch probability among indices in group 2 and 3, 4; p < 0.05;

^c Mismatch probability among indices in group 3 and 4; p < 0.05.

The reliable increasing of the E₂ level by more than 25% and T hormone level by 122% in female offspring born to young mothers with FPI has been observed during sex hormones detecting. The ratio between estradiol and testosterone levels were not differ from intact group of relevant age. The reliable increasing of indices in T/E₂ ratio (p < 0.05) whilst unchanging of E₂ level and slightly increasing of T level (p < 0.05) have been determined in offspring born to mature mothers with FPI.

The ratio between T/E₂ is important for E₂ effects manifestation because E₂ is synthesized in women from T in the adrenal glands cortex, ovarian follicles and in the placenta.

The body masses, relative and absolute organs' masses have been detected and calculated during rat's autopsy. Data obtained dem-

onstrate that the increasing of kidneys masses (p < 0.05) is considered to be the consequence of FPI in young female. The group of offspring born to reproductive mature females with FPI has demonstrated bigger changes of weight indices. The absolute liver and adrenal gland masses were diminished by 17% (p < 0.05), kidneys masses were diminished by 9% compared to intact animals, but mass of pituitary glands hasn't changed (table 2).

As table 3 shows, there wasn't difference of body weight in all tested groups of animals. Thus, the ovarian masses were decreased by 40% in females of second group (p < 0.05) and masses of uterus were reduced twice in females of fourth group (p < 0.05). The number of mature follicles in ovaries of all females has been calculated during autopsy. The decrea-

Table 3

Body weight, absolute and relative masses of uterus and gonads indices in mature offspring of intact and tested mothers, Me \pm s

Group of offspring (n = 7)	Body mass, g	Uterus weight		Ovarian weight	
		Absolute mass, g	Relative mass, %	Absolute mass, g	Relative mass, %
1. Intact from young mothers	150.0 \pm 8.37	0.34 \pm 0.17	0.22 \pm 0.13	0.049 \pm 0.009	0.032 \pm 0.006
2. Offspring of young mothers with FPI	135.0 \pm 35.60	0.40 \pm 0.15	0.29 \pm 0.02	0.030 \pm 0.012 ^a	0.022 \pm 0.007 ^a
3. Intact offspring of mature mothers	150.0 \pm 14.32	0.56 \pm 0.27 ^c	0.33 \pm 0.18	0.042 \pm 0.005	0.028 \pm 0.004 ^b
4. Offspring of mature mothers with FPI	137.0 \pm 4.67	0.27 \pm 0.04 ^a	0.19 \pm 0.02	0.040 \pm 0.006	0.029 \pm 0.004 ^b

Notes:

^a Mismatch probability among indices in group 1 and 2, 3,4; $p < 0.05$;

^b Mismatch probability among indices in group 2 and 3, 4; $p < 0.05$;

^c Mismatch probability among indices in group 3 and 4; $p < 0.05$.

single number of follicles has been determined in the offspring born to young females with FPI (3.00 ± 1.17 compared to 5.00 ± 1.52 in the intact females, ($p < 0.05$)). As for offspring of mature females, there wasn't difference in the number of follicles. There weren't changes in relative masses of spleen and thymus gland in females of all the groups.

The cyclical nature is a particularity of the female reproductive system functioning. The estrus cycle has been registered in all the mature female offspring in both intact groups. The decreasing of the functioning females has been determined: 30 % of offspring born to young mothers with FPI haven't regular estrus cycle ($p < 0.001$); 28% of offspring haven't regular cycle in group of mature reproductive females with FPI. Therefore, the duration and phase structure of the estrus cycle in all tested groups with FPI not much changed.

As shown earlier by our investigation, the intact pregnant females of mature reproductive age have demonstrated decreasing levels of progesterone and estradiol compared to intact young reproductive females. This hormonal status indicates decreasing of the fertilization ability and hormonal homeostasis changes in women's organism with age [16]. Obtained results are proved by literature data, thus in women over 32 years the fertilization ability is gradually decreasing. The ability to be fertilized in women over 45 years practically absents [17].

The substantial declining of progesterone and estradiol levels in young pregnant female rats with FPI has been observed. As shown above, ovaries and egg cells start to form in mother's womb. As shown by our research, low hormonal level in pregnant female influences on egg cells and gonads developing. Offspring have got the less number of follicles and decreased ovarian mass that may cause some problems of fertilization in future life.

As shown earlier by our investigation, the mature rats females with FPI demonstrated similar to intact animals' progesterone and estradiol levels that may testify to triggering off adaptive physiological reactions. However, the shifting of sex hormones ratio to testosterone and decreasing of adrenal glands and uterus masses have been determined in their female offspring.

Increased testosterone level in the follicles fluid causes the strengthening of growing follicles atresia in rat's offspring born to mothers with FPI of both groups of age, which means the inhibition of follicles maturing. Luteinizing hormone may inhibit the androgens synthesizing function of ovaries through their inadequate stimulation. Under the condition of normal menstrual cycle, it is necessary to have strong gonadotropin ratio (luteinizing hormone/ follicles stimulating hormone) for full follicles maturing and ovulation. Increased testosterone level promotes inadequate ovarian sti-

mulation that leads to the steroid genesis disturbances. There are receptors for luteinizing hormone on the membrane of follicle's cell theca interna which begins to synthesize larger quantities of androgens under the condition of increased secretion of luteinizing hormone. The granulosa cells, that include receptors for follicles stimulating hormone, can't metabolize surplus amount of androgens into estrogens in case of follicles stimulating hormone shortage. Therefore, the quantity of estrogens decreases that leads to persistent hyperandrogenia [18, 19].

Increased luteinizing hormone level causes hyperplasia of stroma and theca cells in ovaries and stimulates androgens production, in this way, maintaining substrates supply for peripheral aromatization and chronic anovulation keeping. Thus, our investigations show, that estrus cycle duration and phase structure haven't significant changes in both age groups with FPI, but 30 percents of offspring have irregular estrus cycle, i. e. anovulation. This may lead to endocrine infertility as well as other reproductive disorders.

CONCLUSIONS

1. Under the influence of experimental fetoplacental insufficiency, female offspring born to mothers of young reproductive age have demonstrated changes of the reproductive system. The decreasing of ovaries mass and number of follicles due to their atresia under the influence of high testosterone level have been observed. Therefore, the pathological anovulation caused by disturbances in the hypothalamus-hypophysis-ovary system regulation has developed.
2. Female offspring born to mothers of mature reproductive age with fetoplacental insuffi-

ciency have demonstrated the same reproductive system changes (higher testosterone level, 30 % female offspring with irregular estrus cycles). The increased testosterone level in sex hormones ratio causes inadequate ovaries stimulation with steroid genesis disturbances as a consequence. The strong androgenization under the impact of high luteinizing hormone level has developed.

3. Significant differences of female offspring reproductive system may be explained by their mothers' different hormonal status during pregnancy.

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Embryonic period is the first crucial period of female reproductive system developing. Specifically, at this period egg cells of future woman start forming in her mother's uterine and continue developing up to the moment when mature egg cell merges with sperm cell forming zygote. The connection between mother's organism and fetus during pregnancy depends on placenta condition; the fetoplacental complex is the functional system which provides essential conditions for fetal developing. The disturbances of this complex may cause fetoplacental insufficiency (FPI). Placental structure and functioning may be adapted to different external stressors. In case of failed adaptation or abnormal placental maturing the healthy child birth is under threat and may cause a developing of adult's diseases in future. These days, the number of reproductive-aged women giving birth at later age is growing. This fact influences on the fertilization, pregnancy, delivery, developing and child functioning. The purpose of this investigation was the studying of the influence of FPI long-term consequences on the reproductive system functioning of mature female offspring born to different-aged mothers. Materials. The healthy, mature rat's females-mothers Vistar line, young and mature reproductive age have been used in the investigation. With the aim to receive the offspring, four experimental groups of animals have been formed. The first and the second group were performed by intact animals of relevant age. Rat's females with experimental FPI of young and mature reproductive age have been united into third and fourth groups accordingly. The modeling of FPI has been carried out by daily subcutaneous introduction of 50 % tetrachloromethane oil solution in dose of 2 ml/kg of body weight to females from 12 to 18 day of pregnancy. After offspring birth the reproductive function of rat's females in the age of 3 months has been researched. Results. Under the influence of experimental fetoplacental insufficiency and higher testosterone level, the decreasing of ovaries mass and number of follicles have been observed in female offspring born to mothers of young reproductive age. On the contrary, ovaries mass and number of follicles in female offspring born to mothers of mature reproductive age with FPI and high testosterone level haven't changed compared to intact group. Although, estrus cycles duration and structure haven't changed under the condition of FPI in both age groups, there were offspring with irregular estrus cycles. These changes in the reproductive system of female offspring may lead to endocrine infertility as well as other reproductive disorders.

Key words: fetoplacental insufficiency, young and mature mothers, female offspring, reproductive system.

**СТАН РЕПРОДУКТИВНОЇ СИСТЕМИ
СТАТЕВОЗРІЛИХ САМИЦЬ НАЩАДКІВ, НАРОДЖЕНИХ ВІД МАТЕРІВ
З ФЕТОПЛАЦЕНТАРНОЮ НЕДОСТАТНІСТЮ**

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Першим критичним періодом розвитку жіночої репродуктивної системи є ембріональний період. Саме в цей період яйцеклітини майбутньої жінки починають формуватися ще в утробі її матері та продовжують дозрівати аж до того моменту, коли зріла яйцеклітина зливається зі сперматозоїдом утворюючи зиготу. Взаємозв'язок між організмами матері та плоду протягом усього гестаційного періоду значною мірою залежить від стану плаценти, фетоплацентарний комплекс утворює єдину функціональну систему, що забезпечує необхідні умови для розвитку плода. Порушення цього комплексу може викликати фетоплацентарну недостатність (ФПН). Структура і функція плаценти може адаптуватися до різноманітних зовнішніх стресорів. У разі невдачі адаптації або неадекватного її розвитку, народження здорової дитини знаходиться під загрозою, а в подальшому, це може призвести до розвитку програмування захворювань дорослих. Останнім часом все більш жінок репродуктивного віку народжують дітей у більш пізньому віці. А це в свою чергу, впливає на стан запліднення, вагітності, народження, формування та функціонування дитини. Метою даного дослідження було вивчення впливу віддалених наслідків ФПН на функціонування репродуктивної системи дорослих нащадків жіночої статі які були народжені матерями різного віку. Матеріали та методи. До дослідження залучали здорових статевозрілих самиць-матерів шурів популяції Вістар, молодого та зрілого репродуктивного віку. Для отримання нащадків було сформовано 4 групи: гр. 1 та 2 — інтактні тварини відповідного віку;

гр. 3 та 4 — самки з експериментальною ФПН відповідно молодого та зрілого віку. Моделювання ФПН проводили шляхом щоденного підшкірного введення самицям з 12 по 18 добу вагітності 50 % олійний розчин тетрахлорметану в дозі 2 мл/кг маси тіла. Після народження нащадків була досліджена репродуктивна функція самиць щурів у віці 3 місяців. Результати. Під впливом експериментальної ФПН у нащадків щурів жіночої статі народжених від матерів молодого репродуктивного віку під впливом високого вмісту тестостерону зменшувалась кількість фолікулів та знижувалась маса яєчників. Навпроти, у самиць нащадків народжених від матерів з ФПН зрілого репродуктивного віку на тлі підвищеного рівня тестостерону, кількість фолікулів та вага яєчників залишалися в межах інтактної групи. Хоча тривалість та фазова структура естрального циклу майже не змінювалась на тлі ФПН у двох вікових групах та все ж таки були нащадки, які мали нерегулярний естральний цикл. Такі зміни в репродуктивній системі нащадків в подальшому можуть призвести як до ендокринного безпліддя, так і до інших репродуктивних розладів.

Ключові слова: фетоплацентарна недостатність, молодий і зрілий вік матерів, нащадки жіночої статі, репродуктивна система.

СОСТОЯНИЕ РЕПРОДУКТИВНОЙ СИСТЕМЫ ПОЛОВОЗРЕЛЫХ САМОК ПОТОМКОВ, РОЖДЕННЫХ ОТ МАТЕРЕЙ С ФЕТОПЛАЦЕНТАРНОЙ НЕДОСТАТОЧНОСТЬЮ

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Первым критическим периодом развития женской репродуктивной системы является эмбриональный период. Именно в этот период яйцеклетки будущей женщины начинают формироваться еще в утробе ее матери и продолжают созревать до того момента, когда зрелая яйцеклетка сливается со сперматозоидом образуя зиготу. Взаимосвязь между организмами матери и плода в течение всего гестационного периода в значительной степени зависит от состояния плаценты, фетоплацентарный комплекс образует единую функциональную систему, обеспечивающую необходимые условия для развития плода. Нарушение этого комплекса может вызвать фетоплацентарную недостаточность (ФПН). Структура и функция плаценты может адаптироваться к разнообразным внешним стрессорам. В случае неудачи адаптации или неадекватного ее развития, рождения здорового ребенка находится под угрозой, а в дальнейшем, это может привести к развитию программирования заболеваний взрослых. В последнее время все больше женщин репродуктивного возраста рожают детей в более позднем возрасте. А это в свою очередь, влияет на состояние оплодотворения, беременности, рождения, формирования и функционирование ребенка. Целью данного исследования было изучение отдаленных последствий ФПН на функционирование репродуктивной системы взрослых потомков женского пола, которые были рождены от матерей разного возраста. Материалы и методы. В исследовании использовали здоровых половозрелых самок-матерей крыс популяции Вистар, молодого и зрелого репродуктивного возраста. Для получения потомков было сформировано 4 группы: гр. 1 и 2 — интактные животные соответствующего возраста; гр. 3 и 4 — самки с экспериментальной ФПН соответственно молодого и зрелого возраста. Моделирование ФПН проводили путем ежедневного подкожного введения самкам с 12 по 18 день беременности 50% масляного раствора тетрахлорметана в дозе 2 мл/кг массы тела. После рождения потомков была исследована репродуктивная функция самок крыс в возрасте 3 месяцев. Результаты. Под влиянием экспериментальной ФПН у потомков крыс женского пола, рожденных от матерей молодого репродуктивного возраста под воздействием высокого уровня тестостерона, уменьшалось количество фолликулов и снижалась масса яичников. Напротив, у самок потомков, родившихся от матерей с ФПН зрелого репродуктивного возраста на фоне повышенного уровня тестостерона, количество фолликулов и вес яичников оставались в пределах интактной группы. Хотя продолжительность и фазовая структура эстрального цикла оставалась почти без изменений на фоне ФПН в двух возрастных группах, и все же были потомками, которые имели нерегулярный эстральный цикл. Такие изменения, в репродуктивной системе потомков, в дальнейшем могут привести как к эндокринному бесплодию, так и к другим репродуктивным расстройствам.

Ключевые слова: фетоплацентарная недостаточность, молодой и зрелый возраст матерей, потомки женского пола, репродуктивная система.