# Characteristics of physical and sexual development of girls conceived by assisted reproductive technologies

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*The objective:* to study the characteristics of the physical and sexual development of girls conceived with the help of assisted reproductive technologies (ART).

*Materials and methods.* An examination of 16 teenage girls who were born with the help of ART was carried out. The average age of the girls was $12.0\pm0.45$ (10–13) years. All girls underwent a clinical, functional, hormonal examinations, secondary sexual characteristics were evaluated according to the J. Tanner scale.

Blood levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), dehydroepiandrosterone sulfate (DHEA-S), as well as estradiol (E2), testosterone, levels of thyroid hormones triiodothyronine (T3) and thyroxine (T4) were determined by the radioimmunoassay method on the microspectrophotometer "Stat fax" 303 PLUS USA in the first phase of the menstrual cycle.

To study the functional activity of the liver, fasting glucose level and oral glucose tolerance test, insulin, alanine aminotransferase and aspartate aminotransferase levels were determined. In order to compare the concentration of hormones, 25 teenage girls of the appropriate age who were born from a spontaneous pregnancy and have a physiological health course of the puberty period were additionally examined.

*Results.* According to the ultrasound examination, the length of the right and left ovaries, as well as all echographic indicators, are significantly increased in girls who were born with the help of ART.

A study of hormone levels in teenage girls conceived with ART revealed statistically higher levels of LH ($5.05\pm1.17$ mIU/ml), DHEA-S ($91.9\pm16.93$ μg/dL), E2 ($78.13\pm17.98$ pg/ml), which indicates hyperandrogenism and hyperestrogenism of adrenal origin. At the same time, the fasting glucose level and its level after the oral glucose tolerance test were statistically lower than similar indicators in girls born from a spontaneous pregnancy and with the physiological course of puberty, but the fasting insulin level was higher ($p<0.05$).

*Conclusions.* In girls who were born with the help of assisted reproductive technologies (ART), premature development of secondary sexual characteristics (late precocious puberty) and pronounced hair growth have been identified.

Carbohydrate metabolism, enzymatic activity of the liver and functional activity of the kidneys in girls who were born with the help of ART do not differ from similar indicators of girls who were born from spontaneous pregnancy and with the physiological course of puberty.

*Keywords:* assisted reproductive technologies, in vitro fertilization, puberty, hirsutism, delayed puberty, precocious puberty.

## Особливості фізичного та статевого розвитку дівчат, зачатих за допомогою допоміжних репродуктивних технологій
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*Мета дослідження:* вивчення особливостей фізичного та статевого розвитку дівчат, зачатих за допомогою допоміжних репродуктивних технологій (ДРТ).

*Матеріали та методи.* Проведено обстеження 16 дівчат-підлітків, які народились за допомогою ДРТ. Середній вік дівчат становив $12,0\pm0,45$ (10–13) року. Усім дівчатам проведено клінічне, функціональне, гормональне обстеження, оцінювали вторинні статеві ознаки за шкалою J. Tanner.

Рівні у крові фолікулостимулювального гормону (ФСГ), лютеїнізуючого гормону (ЛГ), тиреотропного гормону (ТТГ), дегідроепіандростерон сульфату (ДГЕА-С), а також естрадіолу (Е2), тестостерону, рівні гормонів щитоподібної залози трийодтироніну (Т3) і тироксину (Т4) визначали радіоімунним методом на мікроспектрофотометрі «Stat fax» 303 PLUS USA у першій фазі менструального циклу.

Для вивчення функціональної активності печінки визначали рівень глюкози натще та за пероральним глюкозотолерантним тестом, рівні інсуліну, аланін-амінотрансферази та аспартатамінотрансферази. З метою порівняння концентрації гормонів додатково обстежено 25 дівчат-підлітків відповідного віку, які народились від спонтанної вагітності та мають фізіологічний перебіг пубертатного періоду.

*Результати.* За даними ультразвукового дослідження, довжина правого і лівого яєчників, а також всі ехографічні показники значно збільшені у дівчат, які народились за допомогою ДРТ.

Дослідження рівнів гормонів у дівчат-підлітків, зачатих за допомогою ДРТ, виявило статистично більші рівні ЛГ ($5,05\pm1,17$ мМО/мл), ДГЕА-С ($91,9\pm16,93$ мкг/дл), Е2 ($78,13\pm17,98$ пг/мл), що свідчить про гіперандрогенію та гіперестрогенію надниркового походження. При цьому рівень глюкози натще та її рівень після перорального тесту

толерантності до глюкози був статистично нижчий за аналогічні показники у дівчаток, народжених від спонтанної вагітності та з фізіологічним перебігом пубертатного періоду, однак рівень інсуліну натще був вищий (p<0,05).

***Висновки.*** У дівчаток, народжених за допомогою допоміжних репродуктивних технологій (ДРТ), визначено передчасний розвиток вторинних статевих ознак (пізнє передчасне статеве дозрівання) та виражене оволосіння.

Вуглеводний обмін, ферментативна активність печінки та функціональна активність нирок у дівчаток, народжених за допомогою ДРТ, не відрізняються від аналогічних показників дівчаток, народжених від спонтанної вагітності та з фізіологічним перебігом статевого дозрівання.

***Ключові слова:*** *допоміжні репродуктивні технології, екстракорпоральне запліднення, статеве дозрівання, гірсутизм, затримка статевого дозрівання, передчасне статеве дозрівання.*

With the increase in the frequency of infertility in recent decades the application of related assisted reproductive technology (ART) methods is increasing year by year. According to data, the incidence of infertility ranges between 10–20% [1–4].

It has been determined that there is a significant increase in the number of children conceived by assisted reproductive technologies as a method of choice in the management of infertility. Over the past 40 years, more than 10 million children have been born using ART. ART use is growing rapidly, with the total number of ART cycles exceeding three million per year, resulting in nearly 500,000 births each year. According to the statistics, 5% of children born in Denmark, 1.7% of children in the United States, one out of every 25 children in Australia, are born by assisted reproductive technology [1, 3].

The health of children born by ART is of interest for researchers. It should be noted, that 23% of parents hide from their children that they were conceived by in vitro fertilization (IVF). It should be noted that the physical development of children born in the initial use of ART is related to premature births and multiple pregnancies [5–8].

Among 5–6-year-old children born by ART, there was difference in the height of girls and boys, in girls it was higher. In the following years, the height of girls is not different from that of boys. According to other information, children born by IVF have a high probability of premature activation of the adrenal glands. An increase in bone age is noted in these girls along with an increase in the amount of luteinizing hormone and dehydroepiandrosterone (DHEA-S) in the blood serum [9–13].

But there are still restricted and contradictory publications about the characteristics of the course of puberty in girls born through ART [14–16]. There is no scientific data about the characteristics of physical and sexual development and the onset of the menstrual cycle in this category of girls. Taking into account the relevance of the problem, the purpose of the present study was determined.

**The objective:** to study the characteristics and course of puberty in girls conceived by assisted reproductive technologies.

## MATERIALS AND METHODS

According to the purpose of the study, 16 adolescent girls conceived by assisted reproductive technology were examined. The average age of the girls was 12.0±0.45 years. The indications for use of ART were infertility of various genesis. The obtained results were compared with the levels of hormones in girls at the same age with physiological course of puberty who born from spontaneous pregnancy and (n=25).

The examination of the girls was carried out with the presence of the mother. All data about course of pregnancy, condition of newborn, physical development and psycho-emotional state of the girls and their achievements in education were studied. Clinical, functional, hormonal, biochemical studies were conducted in all examined girls. According to the scale of J. Tanner, secondary sexual characteristics were evaluated.

Following investigation included, the study of the function of the hypothalamus-pituitary-adrenal-ovarian system, as well as the function of the thyroid gland, blood levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyrotropin hormone (TTH), dehydro-epiandrosterone (DHEA-S) as well as estradiol ($E_2$), testosterone (T), the level of thyroid ($T_3$) and thyroxine ($T_4$) were determined. The level of hormones was determined by the radioimmune method with a micro spectrophotometer «Stat fax 303 PLUS», USA, and using special strip system Dri-Dye, USA, and filter 340 nm during the first phase of the menstrual cycle.

All of the examined underwent an ultrasound examination (USE) with a transabdominal transducer: the length, width, anterior-posterior diameter of the uterus, the angle between the body and the cervix of the uterus, the size and location of the ovaries were studied.

At the same time, fasting glucose and oral glucose tolerance test, level of insulin in blood serum, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were determined in order to study the functional activity of the liver. Glucose was determined by the photometric method on an architect c 8000 device («Abbot», USA). Determination of insulin was conducted by the hemoluminescence method on an architect 1000 Abbot (USA) device.

All the obtained data were statistically analyzed. For each group, the average numerical value (M), the mean square deviation (σ2) of the average numerical value and its standard error (Se), as well as the minimum (min) and maximum (max) values of the series were determined. The average and standard deviation (means) of all data were calculated. The differences were considered statistically significant at P<0.05. Statistical processing was carried out using the «Statgraph» program.

## RESULTS AND DISCUSSION

For the assessment of the severity of hirsutism in all of the examined included in the study, the Ferriman-Galway scale was used. It was determined that the hirsut number in these girls was 20.0±2.31 (13–29). In the comparative group, this indicator was 10.35±0.34 (8–13) points. The study of the development of secondary sexual characteristics revealed that the development of breast according to the J. Tanner scale was 2.4±0.11 (1–3), axillary hair (Ax) was 2.67±0.22 (2–3), pubic hair (P) was 3.33±0.13 (2–4) points.

These indicators were noticeably higher than the similar indicators of the physiological course of sexual devel-

*Table 1*

**Indicators of hormones in girls conceived by assisted reproductive technologies during puberty (M±Se)**

| Hormones | Girls conceived by ART (n=16) | Girls born from spontaneous pregnancy and with physiological course of puberty (n=25) | P -value |
|---|---|---|---|
| FSH, mIU/ml | 4.15±0.63 (3.09–5.88) | 5.89±0.01 (1–8.1) | >0.05 |
| LH, mIU/ml | 5.05±1.17 (2.28–9.78) | 1.54±0.25 (0.9–2.1) | <0.05 |
| TTH, uIU/ml | 1.89±0.36 (1.01–3.03) | 2.8±0.35 (2.1–3.2) | >0.05 |
| Prl, uIU/ml | 265.62±53.73 (130.5–464.4) | - | - |
| T, ng/ml | <0.025 | - | - |
| DHEA-S, ug/dl | 91.9±16.93 (25.39–186.9) | 6.0±2.31 (0.4–11.1) | <0.05 |
| P, ng/ml | <0.050 | - | - |
| $E_2$, pg/ml | 78.13±17.98 (12.89–189.3) | 29.16±1.59 (16.3–60.8) | <0.05 |
| $T_3$, pmol/l | 5.26±0.26 (4.31–6.02) | 1.73±0.28 (1.1–2.3) | <0.05 |
| $T_4$ freet, pmol/l | 14.8±0.93 (11.87–18.8) | 48.5±6.1 (40.6–60.3) | <0.05 |

opment. The results of study of hypothalamus-pituitary-adrenal-ovarian system and thyroid hormones in girls born by ART are presented in table 1.

As shown in the table 1, levels of LH, DHEA-S, and $E_2$ are markedly higher in girls conceived by ART in comparison with girls of the same age, born from spontaneous pregnancy and with physiological course of puberty. At the same time, $T_3$ is statistically significantly higher and $T_4$ is lower in the examined girls. Levels of Testosterone and Progesterone were slightly elevated and have no statistically significance.

Ultrasound examination of the reproductive organs of the examined girls was carried out with a transabdominal probe. The obtained results are presented in Table 2.

As shown, the length of the right ovary increases to a statistically significant degree during puberty in girls born from pregnancy by ART, in the left ovary all the echographic parameters were significantly higher. Biochemical blood indicators of the girls included to the study are presented in a Table 3.

As can be seen from Table 3, the biochemical indicators determined in girls at puberty conceived by ART, correspond to physiological values. At the same time, the level of fasting glucose and its level after oral glucose tolerance test, were statistically lower than the similar indicators in girls born from spontaneous pregnancy and with physiological course of puberty, however level of fasting insulin was higher (p<0.05). It was determined that the indicators of ALT and AST, which reflect the enzymatic activity of the liver, correspond to the physiological values, as well as the levels of creatinine and residual nitrogen.

Currently, data on long-term health risks in children born after ART are still limited, but suggest an increased risk of changes in blood pressure and cardiovascular function. Several large national registries have been established to study the short- and long-term effects of ART treatment in children and their mothers [17–23].

Taking into account children born after ART from the mid-1980s to the present day, such data allow long-term follow-up of children and their mothers to study the risk

*Table 2*

**Echographic indicators of genital organs in girls conceived by Assisted reproductive technologies during puberty**

| Echographic indicators | Girls born from spontaneous pregnancy and with physiological course of puberty (n=25) | Girls conceived by Assisted reproductive technologies (n=16) | P-value |
|---|---|---|---|
| Uterus, mm: | | | |
| – length of the uterine corpus | 42.24±1.11(31–50) | 40.0±1.86 (35–45) | >0.05 |
| – width | 29.12±1.82 (18–45) | 26.83±1.61 (20–37) | >0.05 |
| – antero-posterior diameter | 29.18±1.66 (15–40) | 28.5±1.5 (26–31) | >0.05 |
| Right ovary, mm: | | | |
| – length | 24.24±0.98 (18–27) | 29.5±1.16 (23–37) | <0.05 |
| – width | 19.71±0.90 (13–28) | 20.0±1.1 (16–30) | >0.05 |
| – thickness | 17.35±0.79 (12–24) | 18.7±0.51 (14–26) | >0.05 |
| Left ovary, mm: | | | |
| – length | 24.47±1.33 (15–36) | 30.0±1.1 (25–38) | <0.05 |
| – width | 12.06±0.04 (10–21) | 20.0±0.93 (15–26) | <0.05 |
| – thickness | 16.82±0.06 (10–23) | 18.34±0.61 (12–23) | <0.05 |

*Table 3*

**Biochemical indicators of blood serum in girls conceived by Assisted reproductive technologies during puberty**

| Indicators | Groups | | P-value |
|---|---|---|---|
| | Girls conceived by Assisted reproductive technologies (n=16) | Girls born from spontaneous pregnancy and with physiological course of puberty (n=25) | |
| Fasting glucose, mg/dl | 78.3±0.12 (70–100) | 82.26±0.016 (70–100) | <0.05 |
| Fasting insulin, uIU/ml | 17.06±1.34 (2,93–41,94) | 9.3±0.06 (7.22–16.5) | <0.05 |
| Glucose after OGTT, mg/dl | 100.0±1.26 (88–120) | 110.51±1.25 (86–130) | <0.05 |
| Insulin after OGTT, uIU/ml | 14.56±2,21 (10,12–25,2) | 20.11±0.35 (16–42) | <0.05 |
| ALT, U/L | 9.25±1,32 (5,72–14,03) | - | - |
| AST, U/L | 14.97±0,94 (13,23–18,86) | - | - |
| Residual nitrogen, mg/dl | 6.2±1,9 (3,92–7,45) | - | - |
| Creatinine, umol/l | 48.78±2,34 (48,19–49,37) | - | - |

*Note.* OGTT – oral glucose tolerance test.

of, for example, cardiovascular diseases, mental disorders and malignancies, as well as for children and young people also suffer from pubertal disorders, reproductive health problems and other rarer diseases.

Our study demonstrated that the levels of LH, DHEA-S, E2 in vast majority of the examined are statistically significantly higher, which indicates hyperandrogenism and hyperestrogenia of adrenal origin. These results differed from other works.

So, Klemetti R, et al studied 122,321 singleton children conceived after ART, and more than 6 million singleton children from the background population, a total of 37,869 children were identified with diagnoses related to disorders of puberty, of which 603 were born after ART. Children conceived after ART had a higher risk of early puberty and late puberty: girls had higher diagnoses associated with early puberty (aHR 1.46; 95% CI: 1.29–1.66) and boys had higher diagnoses associated with late puberty (aHR 1.55; 95% CI: 1.24–1.95) [24].

F. Belva, et al. studying anti-Mullerian hormone (AMH), FSH, LH and DHEAS in women born with ICSI and their spontaneously conceived peers, revealed that in these patients, the levels of circulating reproductive hormones, including AMH, FSH, LH and DHEAS, were similar to those of peers born after spontaneous conception [25].

Epigenetic changes have been proposed as underlying mechanisms for the observed adverse health effects in ART-conceived offspring [26, 27].

ART manipulations occurring very early in development, which is characterized by extensive epigenetic reprogramming, can indirectly alter the normal development and long-term health consequences of these offspring [28, 29].

However, to date there is no consensus on whether the potential differences observed in ART offspring are due to the laboratory methods used in ART or perhaps to the intrinsic characteristics of the infertile couple [30].

## CONCLUSION

In girls conceived by assisted reproductive technologies there are increased hair growth during puberty (hirsutism), premature development of secondary sexual characteristics (delayed precocious puberty), inappropriately to the age more than normal developed breast. According to the ultrasound examination, the length of the right ovary, the length of the left ovary, and all echographic indicators are significantly increased. The average levels of LH (5.05±1.17 miU/ml), DHEA-S (91.9±16.93 ug/dl), $E_2$ (78.13± 17.98 pg/ml) are statistically significantly higher in girls born by assisted reproductive technology, which indicates hyperandrogenism and hyperestrogenia of adrenal origin.

Carbohydrate metabolism, enzymatic activity of the liver and functional activity of the kidneys in girls conceived by use of assisted reproductive technology do not differ from those born from spontaneous pregnancy and with physiological course of puberty.

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## REFERENCES

1. European Society of Human Reproduction and Embryology. ART fact sheet 2022 [Internet]. 2022. Available from: https://www.eshre.eu/-/media/ sitecorefiles/Press-room/ESHRE_ARTFactSheet_2022.pdf?la=en&hash=223AA F16CEC0EC6510EB371B52BE-10384892AF49.

2. European IVF-monitoring Consortium (EIM)‡ for the European Society of Human Reproduction and Embryology (ESHRE); Wyns C, Bergh C, Calhaz-Jorge C, De Geyter C, et al. ART in Europe, 2016: results generated from European registries by ESHRE. Hum Reprod Open. 2020;2020(3):hoaa032. doi: 10.1093/hropen/hoaa032.

3. Sunderam S, Kissin DM, Zhang Y, Jewett A, Boulet SL, Warner L, et al. Assisted Reproductive Technology Surveillance − United States, 2017. MMWR Surveill Summ. 2020;69(9):1-20. doi: 10.15585/mmwr.ss6909a1.

4. Perkhulyn OM, Pakharenko LV, Sukhin VS, Saltovskiy OV, Kovalchuk VM, Hranovska HI, Kravchenko OV. Evaluation of hormonal function in women with cervical insufficiency and infertility in the history. Wiad Lek. 2021;74(10):2412-6.

5. Carlsen EØ, Wilcox AJ, Magnus MC, Hanevik HI, Håberg SE. Reproductive outcomes in women and men conceived by assisted reproductive technologies in Norway: prospective registry based study. BMJ Med. 2023;2(1):e000318. doi: 10.1136/bmjmed-2022-000318.

6. Qin JB, Sheng XQ, Wu D, Gao SY, You YP, Yang TB, et al. Worldwide prevalence of adverse pregnancy outcomes among singleton pregnancies after in vitro fertilization/intracytoplasmic sperm injection: a systematic review and meta-analysis. Arch Gynecol Obstet. 2017;295(2):285-301. doi: 10.1007/s0 0404-016-4250-3.

7. Luke B. Pregnancy and birth outcomes in couples with infertility with and without assisted reproductive technology: with an emphasis on US population-based studies. Am J Obstet Gynecol. 2017;217(3):270-81. doi: 10.1016/j. ajog.2017.03.012.

8. Raatikainen K, Kuivasaari-Pirinen P, Hippeläinen M, Heinonen S. Comparison of the pregnancy outcomes of subfertile women after infertility treatment and in naturally conceived pregnancies. Hum Reprod. 2012;27(4):1162-9. doi: 10.1093/humrep/des015.

9. Hart R, Norman RJ. The longer-term health outcomes for children born as a result of IVF treatment: Part I-General health outcomes. Hum Reprod Update. 2013;19(3):232-43. doi: 10.1093/humupd/dms062.

10. Chen M, Heilbronn LK. The health outcomes of human offspring conceived by assisted reproductive technologies (ART). J Dev Orig Health Dis. 2017;8(4):388-402. doi: 10.1017/S2040174417000228.

11. Lu YH, Wang N, Jin F. Long-term follow-up of children conceived through assisted reproductive technology. J Zhejiang Univ Sci B. 2013;14(5):359-71. doi: 10.1631/jzus.B1200348.

12. Henningsen AA, Bergh C, Skjaerven R, Tiitinen A, Wennerholm UB, Romundstad LB, et al. Trends over time in congenital malformations in live-born children conceived after assisted reproductive technology. Acta Obstet Gynecol Scand. 2018;97(7):816-23. doi: 10.1111/aogs.13347.

13. Doulgeraki T, Iliodromiti S. Reproductive outcomes in women and men conceived by assisted reproductive technologies. BMJ Med. 2023;2(1):e000547. doi: 10.1136/bmjmed-2023-000547.

14. Golyanovsky O, Zukin V, Shemyakina N, Rubinstein A. Features of the course of pregnancy, childbirth and postpartum period against the background of the use of assisted reproductive technologies. Reprod Health Women. 2021;(9-10):79-87. doi: 10.30841/2708-8731.9-10.2021.252598.

15. Rubinstein A. Tactics of pregnancy, childbirth and postpartum management in patients of late reproductive age with pregnancy that occurred with the help of assisted reproductive technologies. Reprod Health Women. 2022;(4):16-22. doi: 10.30841/2708-8731.4.2022.262761.

16. Safarova A. The role of clinical and immunological factors in the results of in vitro fertilization in women. Reprod Health Women. 2023;(7):69-73. doi: 10.30841/2708-8731.7.2023.292603.

17. Mustafayeva IR, Aliyeva EM. Features of the formation of reproductive function during puberty. Textbook, Baku; 2022. 163 p.

18. Purkayastha M, Roberts SA, Gardiner J, Brison DR, Nelson SM, Lawlor D, et al. Cohort profile: a national, population-based cohort of children born after assisted conception in the UK (1992-2009): methodology and birthweight analysis. BMJ Open. 2021;11(7):e050931. doi: 10.1136/bmjopen-2021-050931.

19. Stern JE, Liu CL, Hwang SS, Dukhovny D, Diop H, Cabral H. Contributions to prematurity of maternal health conditions, subfertility, and assisted reproductive technology. Fertil Steril. 2020;114(4):828-36. doi: 10.1016/j.fertnstert.2020.03.036.

20. Spector LG, Brown MB, Wantman E, Letterie GS, Toner JP, Doody K, et al. Association of In Vitro Fertilization With Childhood Cancer in the United States. JAMA Pediatr. 2019;173(6):e190392. doi: 10.1001/jamapediat rics.2019.0392.

21. Fauque P, De Mouzon J, Devaux A, Epelboin S, Gervoise-Boyer MJ, et al. Do in vitro fertilization, intrauterine insemination or female infertility impact the risk of congenital anomalies in singletons? A longitudinal national French study, Human Reproduction. 2021;36(3):808-16. doi: 10.1093/humrep/ deaa323.

22. Lemardeley G, Pirrello O, Dieterlé S, Zebina A, Astrugue C, Jonveaux P, et al. Overview of hospitalizations in women undergoing oocyte retrieval for ART in the French national health data system. Hum Reprod. 2021;36(10):2769-81. doi: 10.1093/humrep/deab147.

23. Spaan M, van den Belt-Dusebout AW, van den Heuvel-Eibrink MM, Hauptmann M, Lambalk CB, Burger CW, et al. Risk of cancer in children and young adults conceived by assisted reproductive technology. Hum Reprod. 2019;34(4):740-50. doi: 10.1093/humrep/dey394.

24. Klemetti R, Perry B, Henningsen AKA, Spangmose AL, Pinborg A, Opdahl S, et al. Puberty disorders among ART-conceived singletons: a Nordic register study from the CoNARTaS group. Hum Reprod. 2022;37(10):2402-11. doi: 10.1093/humrep/deac192.

25. Belva F, Roelants M, Vloeberghs V, Schiettecatte J, Evenepoel J, Bonduelle M, et al. Serum reproductive hormone levels and ultrasound findings in female offspring after intracytoplasmic sperm injection: first results. Fertil Steril. 2017;107:934-9.

26. Huntriss J, Balen AH, Sinclair KD, Brison DR, Picton HM; Royal College of Obstetricians Gynaecologists. Epigenetics and Reproductive Medicine: Scientific Impact Paper No. 57. BJOG. 2018;125(13):43-54. doi: 10.1111/1471-0528.15240.

27. Jiang Z, Wang Y, Lin J, Xu J, Ding G, Huang H. Genetic and epigenetic risks of assisted reproduction. Best Pract Res Clin Obstet Gynaecol. 2017;44:90-104. doi: 10.1016/j.bpobgyn.2017.07.004.

28. Cantone I, Fisher AG. Epigenetic programming and reprogramming during development. Nat Struct Mol Biol. 2013;20(3):282-9. doi: 10.1038/nsmb.2489.

29. El Hajj N, Haaf T. Epigenetic disturbances in vitro cultured gametes and embryos: implications for human assisted reproduction. Fertil Steril. 2013;99(3):632-41. doi: 10.1016/j.fertnstert.2012.12.044.

30. Berntsen S, Söderström-Anttila V, Wennerholm UB, Laivuori H, Loft A, Oldereid NB, et al. The health of children conceived by ART: 'the chicken or the egg?'. Hum Reprod Update. 2019;25(2):137-58. doi: 10.1093/humupd/ dmz001.