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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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Содержание:

FERTILITY FUNCTIONS IN 4VHPV VACCINATED ARMENIAN COHORT

Vahe Ashot Ter-Minasyan.

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Abstract.

Introduction: Despite being highly preventable, cervical cancer (CC) is the eighth most prevalent form of female cancer in Armenia and the second most common malignancy among those aged 15 to 44. In Armenia, there is an age-standardized incidence of 7.8 per 100,000 females, and an age-standardized mortality of 4.6 per 100,000 females. Globally, the CC is the 4th most common cancer among women. Its incidence was 604,127 new cases and 341,831 deaths in 2020.

We conducted a retrospective, observational cohort study using clinical data to verify the influence of HPV vaccine (Gardasil, Merck&CO) on fertility function in women, vaccinated in RA since 2017 year in the limits of anti-HPV vaccination Program (included in National Vaccination Calendar).

Materials and Methods: For the study, we analyzed data received from Armenian-American Wellness Center (Yerevan, Armenia). 98 female volunteers vaccinated with the 4vHPV who attended AAWC and were examined for reproductive function. The subjects were divided into 3 age groups – 1st group – 15 years -24 years 11 months, 2nd group - 25 years -34 years 11 months, 3rd group - 35 -40 years.

Each control group was composed of randomly selected 30 healthy women in age identical to the main group who applied AAWC for regular checkup in the same time frame and have never been exposed to anti HPV vaccine.

Results: The current research is aimed to reveal any negative impact of 4vHPV vaccine on fertility indicators in Armenian cohort. The performed comparative statistical analysis of the assessed indicators has revealed the ORs<1 for POI, late fertilization disorders of menstrual cycle and anovulation prevalence indicators. The chance of investigated disorders' development in 4vHPV vaccine exposed cohort did not exaggerate that in non-exposed sample cohort.

The significant difference was not observed in Anti-Mullerian Hormone, FSH basal levels, as well as in mean ovarian volume and number of antral follicles indicators between clinical and respective control groups ($p < .05$).

Conclusion: The data obtained make us to conclude about absence of any negative impact of 4vHPV vaccine on fertility function indicators in 4vHPV vaccinated cohort in RA. The study results contribute to perception of the 4vHPV vaccine safety concept, what in its turn can trigger increase of vaccination coverage leading to CC control efficiency.

Key words. HPV, vaccination, papillomavirus, efficacy, safety, fertility.

Introduction.

Despite being highly preventable, cervical cancer (CC) is the eighth most prevalent form of cancer in women in Armenia and the second most common malignancy among those aged 15 to 44. In Armenia, there is an age-standardized incidence of 7.8 per 100,000 females, and an age-standardized mortality of 4.6 per 100,000 females (or 115 fatalities in 2020) [1]. Globally, the CC is the 4th most common cancer among women. Its prevalence was estimated 604,127 new cases and 341,831 deaths in 2020 [2].

High HPV vaccination rates among girls of the appropriate age may contribute to effectiveness of CC preventive. This is essential to achieve the WHO's 2020 target of 4 cases per 100,000 female population [1,3]. The strongest evidence for the value of vaccination as a main preventive intervention against cancer is the declining incidence of precancerous diseases and malignancies, as confirmed by screening, which in turn leads to a decline in CC mortality rates [4,5].

The 4-valent vaccine-type HPV detection rate among not vaccinated women decreased from 32.4% to 19.4% (a 40% decrease; odds ratio of 0.50, 95% confidence interval of 0.26 to 0.97). The HPV trends in US community within >10 years post 4-valent HPV vaccine and post 9-valent vaccine period were investigated. The evidence of vaccine effectiveness and herd protection was determined.

However, ambiguous data exist concerning the safety of the quadrivalent HPV vaccine in context of its outcomes. Some data from different sources published contain the evidence of arguable influence of HPV vaccine exposure on fertility functions and pregnancy outcome.

HPV vaccination (with Gardasil, Merck&CO approved by WHO) was included in the National Immunization Calendar for females aged 13 since December 2017 and was then expanded to include females aged 13-45 and males aged 14-45 starting in February 2019. HPV vaccination coverage rates in 2021 and 2022 were 10.8% and 13.3% respectively and increased to 23.7% for the period from January to April 2023 (girls aged ≤15, last dose) [6].

The data regarding prevalence of fertility disorders in anti HPV vaccine exposed cohort is not sufficient to judge about its impact on fertility functions. There is a significant lack of data presenting the impact of vaccination on fecundability in Armenian population.

All mentioned above stipulated us to undertake the research, aimed to verify the influence of HPV vaccine (Gardasil, Merck&CO) on fertility indicators in women, vaccinated in RA since 2017 year in the limits of anti-HPV vaccination program (included in National Vaccination Calendar).

Materials and Methods.

For the study, we analyzed data contributed by AAWC (Armenian-American Wellness Center).

98 female volunteers vaccinated with the 4vHPV vaccine were invited to AAWC and examined for reproductive function.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in the approval by human research committee. All participants gave written informed consent to participate in the trial and to use their data.

The protocol was approved by the Ethics Committee of Named after S.Kh.Avdalbekyan National Institute of Health, RA MOH (Yerevan, Armenia). The subjects were divided into 3 age groups – 1st group - 15-24 years 11 months, 2nd group - 25-34 years 11 months, 3rd group - 35-40 years.

Every control group was composed of randomly selected 30 healthy women in age identical to the main group who attended AAWC for regular checkup in the same time frame and have never been exposed to anti HPV vaccine.

The criteria of inclusion were the following:

1) 15-40 years women,

2) who received a 4Vhpv vaccine (both doses) in the maximally 6 months period prior to their last menstrual period (LMP).

Exclusion criteria were the following:

- secondary (hypothalamic) amenorrhea
- hyperprolactinemia
- polycystic ovary syndrome (atypical form)
- obesity
- surgical interventions

Statistical data processing.

Statistical data processing was performed using the statistical software package SPSS 23 (Statistical Package for Social Science 23) to determine any significant difference in the clinical characteristics and rates of fertility function disorders between the groups. The Odds Ratio was calculated to reveal the measure of association between a 4vHPV vaccine exposure and its impact on clinical characteristics of the cohorts. For a comparative analysis of fertility functions indicators between the means of clinical and control groups the Kolmogorov-Smirnov test was used followed by the Student's parametric tests. The chosen level of significance was at 0.05 with CI 95%.

Results.

The Social-demographic Characteristics of the Study Participants.

Socio-demographic indicators among the cohort are represented in Table 1. Average age of the study sample was 20.2±3.1, 29.2±4.2 and 36.9±2.5 years old correspondingly in 1st, 2nd and 3rd clinical groups. The BMI was 22.2±2.6, 23.6±1.4 & 25.4±2.1 kg/m^2 correspondingly in 1st, 2nd and 3rd clinical groups, what approximately correspondents to the highest limit of the normal weight. There was no observed reliable difference between the indices of the clinical and appropriate control groups. The dominating marital status was "married" in all clinical and control groups. The prevalence of married status was 26 (66.7%), 25 (69.4%) and 14 (60.8%) correspondingly in 1st, 2nd and 3rd clinical groups. The strong difference was revealed in these indicators between patients of 1st clinical and 1st control groups (p-value>.05). More than half of the investigated cohort (76 (77.5%)) had at least 1 child. The prevalence of children presence in family was 30 (76.9%), 26 (72.2%) and 20 (66.7%) correspondingly in 1st, 2nd and 3rd clinical groups. The strong difference was revealed in these indicators between patients of 3rd clinical and 3rd control groups (p-value>.05).

Clinical characteristics in HPV vaccinated and non-vaccinated groups.

The data concerning relationship between fertility function indicators and vaccine exposure in the investigated cohort are represented in the Table 2. The fertility functions characteristics were compared between exposed (post-exposure period) and non-exposed cohort.

GROUP I.

The preterm ovarian insufficiency was revealed in 1(2.56%) case among 39 exposed patients and 1(3.3%) cases among 30 patients of control group (OR = 0.763; 95% CI [0.046 - 12.723], p = .850). The POI prevalence indicators have not demonstrated significant difference between clinical group I and control group I.

The **late fertilization** had the identical rate (in 1(2.56%) among 39 exposed patients and 1(3.3%) cases among 30 patients of control group) without any reliable difference between clinical and control groups (OR = 0.763; 95% CI [0.046 - 12.723], p = .850).

Menstrual cycle disorders were reported in 4 (10.3%) cases in clinical group I and 4 (13.2%) cases of control group I; The prevalence indicators of Menstrual cycle disorders as well were not characterized by reliable difference (OR = 0.742; 95% CI [0.170 - 3.250], p = .693) between exposed and non-exposed cohorts.

The Anovulation prevalence indicators also were 2(5.1%) and 2(6.6%) correspondingly in clinical and control group I. No essential difference between exposed and non-exposed cohorts was observed; OR = 0.757; 95% CI [0.100–5.708], p = .787).

Table 1. *The Social-demographic characteristics of the Study Participants' Sample.*

Characteristics	Group I (n=39)	Group 2 (n=36)	Group 3 (n=23)	Control Group I (n=30)	Control Group 2 (n=30)	Control Group 3 (n=30)
Age, years	20.2±3.1	29.2±4.2	36.9±2.5	21.3±2.9	31.4±3.0	37.7±2.9
BMI	22.2±2.6	23.6±1.4	25.4±2.1	22.4±2.2	±24.0±2.3	224.9±2.0
Marrital Status*						
Married or living together, n (%)	26 (66.7%)	25 (69.4%)	14 (60.8%)	17 (56.7%)	20 (66.7%)	19 (63.3%)
Single, divorced or widowed n (%)	14 (35.9%)	12 (33.3%)	9 (39.1%)	13 (43.3%)	10 (33.3%)	11 (36.7%)
Children,** n (%)	30 (76.9%)	26 (72.2%)	20 (66.7%)	26 (86.6%)	23 (76.7%)	14 (46.7%)

** The strong difference was observed between groups 1 control group I (P_{1-2} <.05).*

***The strong difference was observed between groups 3 and control group 3 (P_{1-3} <.05).*

Table 2. *Comparison of clinical characteristics in 4vHPV vaccinated and non-vaccinated groups.*

Variable	Group I (n= 39)	Group 2 (n= 36)	Group 3 (n= 23)	Control Group I (n=30)	Control Group 2 (n=30)	Control Group 3 (n= 30)	Statistical indicator	Group I Vs Control 1	Group 2 Vs Control 2	Group 3 Vs Control 3
POI	1(2.6 %)	1 (2.8 %)	0 (0.0%)	1 (3.3 %)	1 (3.3%)	1 (3.3 %)	*OR*	0.763	0.829	0.418
							95%CI	[0.046 - 12.723]	[0.050- 13.834]	[0.016 -10.751]
							p-value	.850	.896	.599
Late fertilization	1 (2.6 %)	2 (5.6 %)	1 (4.35 %)	1 (3.3 %)	2 (6.6%)	3 (9.9 %)	*OR*	0.763	0.823	0.409
							95%CI	[0.046 - 12.723]	[0.109 - 6.225]	[0.040 - 4.214]
							p-value	.850	.851	.453
MC Disorders	4 (10.3%)	7 (19.6%)	5 (21.7%)	4 (13.2%)	7 (23.1%)	7 (23.1%)	*OR*	0.742	0.793	0.913
							95%CI	[0.170 - 3.250]	[0.243 - 2.587]	[0.248 - 3.359]
							p-value	.693	.701	.891
Anovulation	2 (5.1%)	3 (8.4 %)	2 (8.7%)	2 (6.6%)	3 (9.9%)	3 (9.9 %)	*OR*	0.757	0.818	0.875
							95%CI	[0.100 - 5.708]	[0.152 - 4.386]	[0.131 - 5.606]
							p-value	.787	.815	.872

Table 3. *Statistical data on hormonal indicators' comparison in HPV vaccinated and non-vaccinated groups.*

Variable	Group I N=39	Group 2 N=36	Group 3 N=23	Control 1 (Non-vaccinated) N=30	Control 2 (Non-vaccinated N=30)	Control 3 (Non-vaccinated N=30)	Statistical indicator	Group I vs Control 1	Group 2 vs Control 2	Group 3 vs Control 3
Basal FSH, mIU/mL	8.43±3.98	9.99±3.34	7.80 ±2.71	8.13±4.24	10.99±3.45	7.89 ±3.01	*t-value*	0.381	0.545	0.926
							p value	.705	.587	.359
							95%CI	[-1.685; 2.285]	[-0.674; 2.674]	[-1.515; 1.695]
Anti-Mullerian hormone	2.69±1.02	2.01±1.20	1.98±0.96	2.65±0.89	2.20±0.86	1.88±1.0	*t-value*	0.536	1.179	0.073
							p value	.594	.243	.942
							95%CI	[-0.428; 0.508]	[-0.333; 0.74]	[-0.44, 7; 0.647]
Antral follicles' number	26.2±4.2	20.4±3.9	13.7±3.7	25.0±4.7	19.8±4.4	12.9±2.1	*t-value*	1.038	1.203	0.153
							p value	.303	.233	.879
							95%CI	[-0.944, 3.344]	[-1.442, 2.642]	[-0.814, 2.414]
Mean ovarian volume	8.1±3.0	7.6±2.3	9.2±3.6	7.9±2.9	8.7±2.4	8.9±4.6	*t-value*	0.295	1.700	1.612
							p value	.769	.094	.111
							95%CI	[-1.067; 1.467]	[-0.979; 1.579]	[-2.036; 2.636]

GROUP 2.

The **POI** was revealed in 1 (2,8 %) case among 36 exposed patients and 1 (3.3%) cases among 30 patients of control group (OR = 0.829; 95% CI [0.050- 13.834], p = .896). There was no significant difference in age group I in the preterm ovarian insufficiency prevalence indicators between clinical and control groups.

The late fertilization had higher prevalence compared to the previous indicator (2 (5.6%) cases in 36 vaccinated patients and 2 (6.6%) cases among 30 patients of control group II without any reliable difference between exposed and non-exposed cohorts (OR = 0.823; 95% CI [0.109 - 6.225], p = .851).

7 (19.6%) cases of Menstrual cycle disorders were registered in clinical group II and 7 (23.1%) - in control group II. No strong difference was observed as well between vaccinated and non-vaccinated patients in this age frame (OR = 0.793; 95% CI [0.243 - 2.587], p = .701).

The Anovulation prevalence indicators also were not characterized by significant difference: 3 (8.4 %) cases were registered among patients of clinical group II and 3 (9.9%) cases - in patients of control group II (OR = 0.818; 95% CI [0.152 - 4.386], p = .815).

GROUP 3.

There was not revealed case of POI - 0 (0%) in clinical group III (n=23) while 1 case in corresponding control group was registered (OR= 0.418; 95% CI [0.016 - 10.751, p = .599).

The prevalence indicators of **Late fertilization, Menstrual cycle disorders** and **Anovulation** did not demonstrate any

reliable difference between clinical and control groups III (OR = 0.409; 95% CI [0.040 - 4.214], p = .453; OR = 0.913; 95% CI [0.248 – 3.559], p = .891 and OR = 0.875; 95% CI [0.131 – 5.606], p = .872 correspondingly for Late fertilization, Menstrual cycle disorders and Anovulation data categories).

Fertility function characteristics in HPV vaccinated and non-vaccinated groups.

The Statistical data obtained regarding the fertility indicators' comparison in HPV vaccinated and non-vaccinated groups are represented in the Table 3. As it is shown in the Table3, exposure to the quadrivalent HPV vaccine was not associated with reliably increased risk of fertility indicators' abnormality.

GROUP I.

The level of **Basal FSH** was average 8.43±3.98 and 8.13±4.24 correspondingly for clinical group I and control group I. There was no significant difference for basal FSH level indices of exposed patients compared to non-exposed cohort (p=.705, t=0.381, 95% CI [-1.685; 2.285]).

The **AMH levels'** indicators also have not demonstrated significant difference between control and clinical groups I (2.69±1.0 and 2.65±0.89 correspondingly for clinical group I and control group I, t=0.536, p=.594, 95% CI [-.428; 0.508]).

The mean number of counted antral follicles in clinical group I was 26.2±4.2 and there was no significant difference compared with the control group I with average amount of 25.0±4.7 (p=.303, t=1.038, 95% CI [-0.944, 3.344]).

The significant difference was not also observed in mean ovarian volume indicators (8.1±3.0 for exposed patients of group I vs 7.9±2.0 for unexposed patients of control group I) (p=.769, t=0.295, 95% CI [-1.067; 1.467]).

GROUP 2.

The indicators of basal **FSH** were 9.99±3.34 and 10.99±3.45 correspondingly for clinical and control groups II. There was no significant difference for basal **FSH level** of exposed patients compared to non-exposed cohorts of group II (p=.587, t=0.545, 95% CI [-0.674; 2.674].

The AMH levels' indicators were 2.01±1.20 vs 2.2±0.86 respectively in clinical group II and control group II. These indicators also have not demonstrated strong difference between control and clinical groups II (p=.243, t=1.179, 95% CI [-0.333; 0.74].

The average count of antral follicles was 26.2±4.2 vs 25.0±4.7 correspondingly for vaccinated and non-vaccinated cohorts in this age-frame). There was no significant difference between clinical group II and control group II (p=.233, t=1.203, 95% CI [-1.442; 2.642]).

The mean ovarian volume indicators were 7.6±2.3 for exposed patients of group II and 8.7±2.4 for unexposed patients of the same age frame. The significant difference was not observed in mean ovarian volume indicators between clinical and control groups II (p=.094, t=1.700, 95% CI [-0.979; 1.579]).

GROUP 3.

The average levels of basal **FSH** were respectively 7.8 ±2.71 and 7.89±3.01 in clinical and control group III. No significant difference for basal **FSH levels** of exposed patients compared to non-exposed cohort was observed (p=.359, t=0.926, 95% CI [-1.515; 1.695]).

The **AMH levels'** indicators (1.98±0.96 vs 1.88±1.0) also have not demonstrated significant difference between clinical and control group III (p=.942, t=0.073, 95%CI [-0.44, 7; 0.647].

The average count of antral follicles was respectively 13.7±3.7 and 12.9±2.1 in exposed and non-exposed patients. These indices were not characterized by reliable difference between group III and control group III (p=.879, t=0.153, 95%CI [-0.814; 2.414]).

The mean ovarian volume indicators were 9.2±3.6 for exposed patients of group III and 8.9±4.6 for unexposed patients of the same age frame. The significant difference was not observed in mean ovarian volume between clinical and control groups III (p=.111, t=1.612, 95% CI [-2.036; 2.636]).

Discussion.

HPV is a persisting condition that can lead to serious complications including carcinomas. In published multiple researches with great observational cohorts it was shown that the inadvertent administration of 4vHPV was effective in terms of significant decrease of CC incidence [7,8].

HPV vaccination has no effect on fertility, no confirmed cases of primary ovarian failure among HPV vaccine recipients in the United States was revealed in accordance with USA Vaccination Adverse Event Reporting Registration system (VAERS), 2014–2017. The research includes the following up of 28 million vaccine doses injected to males and females with 7244 reports of undesirable reactions (259 reports per 1,000,000 doses). 97.4% of these had non-serious character (dizziness, headache, injection site reactions), 3 messages comparable to diagnosis of primary ovarian failure – were not confirmed [9]. No unusual or expected manifestations after vaccination were revealed. The incidence of serious manifestations, including primary ovarian failure, was within the observed range during the period before the introduction of the HPV vaccine [10].

The data received via prospective study - follow-up of 996,300 adolescent girls and young women aged 11-34 years from 2007 to 2016 revealed the identical frequency of POI with complete absence of its association with vaccination against HPV [11].

A comparison of the average probability of fertilization was made in a study of vaccinated and non-vaccinated women, including 3,483 women planning pregnancy, and 1,222 of their partners over a 12-month follow-up period. The results showed that HPV vaccination had no effect on the ability to get pregnant. The researchers evaluated fertility and 95% confidence intervals (CI) for pre - HPV vaccination Pap test. Data obtained revealed that patients with history of STD & PID (risk group of HPV), had higher post vaccination fertility than those not vaccinated (FR=1.35, 95% CI: 0.99, 1.86). Authors concluded that anti HPV vaccine is positively associated with fecundability in women with positive STD history in spite of the fact that it had insignificant general effect on fecundability [12].

On the other hand, data of some researchers were published regarding HPV vaccine impact on fertility indicators [13,14]. However, the overwhelming majority of data indicate the absence of any association between 4vHPV and increased risks of fertile function disorders. Particularly noteworthy are the data published by WHO and special task forces of US preventive services, as well as the authors of multi center studies

in European countries, devoted to a comparative analysis of the clinical effectiveness of various vaccination programs in countries with different income levels. Our preliminary data indicates that Armenian females exposed to 4vHPV in their distal (1 year before pregnancy) or pre-pregnancy (8 weeks before pregnancy) periods within limits of National HPV vaccination program didn't demonstrate reliable discrepancy in APO (Adverse pregnancy outcomes) risk incidences compared with the non-exposed individuals. The data of performed comparative statistical analysis of the assessed indicators has revealed the ORs<1 for APOs' indicators. The chance of investigated APOs development in anti HPV vaccine exposed cohort was not higher than in non-exposed sample cohort. The ORs>1 in Live birth in term (1.2544 & 1.1338 correspondingly for pre-pregnancy and distal exposure indicators) are the evidence of comparatively higher (exaggerating) probability for Live birth in term in exposed cohort.

The current research is directed to reveal any negative impact of 4vHPV vaccine on fertility indicators in Armenian cohort. The performed comparative statistical analysis of the assessed indicators has revealed the ORs<1 for POI, late fertilization disorders of menstrual cycle and anovulation prevalence indicators. The chance of investigated disorders' development in 4vHPV vaccine exposed cohort was not higher than in non-exposed sample cohort.

Thus, the results of current research didn't demonstrate reliable discrepancy in fertility indices in HPV vaccinated and non-vaccinated cohorts of Armenian females. The data obtained are in compliance with the results of multiple studies devoted to the efficacy and safety of 4vHPV vaccine in reproductive age frame female population [15-17].

The limitation of our study is the unengaged group of women who had vaccinations and are likely sterile. We were also constrained by the small number of research group members, explained by the Armenia's ongoing poor vaccination program coverage.

Conclusion.

The data obtained make us to conclude about absence of any negative impact of 4vHPV vaccine on fertility function indicators in 4vHPV vaccinated cohort in RA. The study results contribute to perception of the 4vHPV vaccine safety concept, what in its turn can trigger increase of vaccination coverage, leading to CC control efficiency.

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