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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.

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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:

Yevchuk YuI, Rozhko MM, Pantus AV, Yarmoshuk IR, Pantus PV.
ANALYSIS OF THE CLINICAL EFFECTIVENESS OF USING THE CREATED COMBINED FIBRIN-BONE SCAFFOLD FOR THE RECONSTRUCTION OF BONE TISSUE DEFECTS OF THE JAWS…….....……6-13

Anton Yu. Postnov, Tatiana V. Kirichenko, Yuliya V. Markina, Petr V. Chumachenko, Andrey V. Suslov, Alexandra G. Ivanova, Eduard R. Charchyan, Alexander M. Markin.
INFLAMMATORY FACTORS IN DISSECTION OF THORACIC AORTIC ANEURYSM…….....……14-17

Gohar Arajyan, Qristine Navoyan, Nvard Pahutyan, Hovhannes Hunanyan, Anahit Pogosyan, Hrachik Gasparyan.
COMPREHENSIVE STUDY OF ANTIOXIDANT ACTIVITY OF OXALIC ACID DIAMIDE DERIVATIVES AND THEIR EFFECT ON THE CONCENTRATION OF MALONIC DIALDEHYDE IN THE BRAIN AND LIVER TISSUES OF WHITE RATS…….....18-23

Nino Abesadze, Jenaro Kristesashvili, Arsen Gvenetadze.
LOW 25OHD IN ENDOMETRIOSIS- RISK FACTOR OR CONSEQUENCE?!.....24-31

Stepanyan L, Lalayan G.
STRESS RESILIENCE AND DECISION-MAKING UNDER PRESSURE: ENHANCING ATHLETIC PERFORMANCE IN COMPETITIVE SPORTS…….....……32-37

Hasan M. Abed, Abdulameer M. Hussein, Sabah N. Jaber.
ENDOVASCULAR INTERVENTIONS: A NEW INSIGHTS AND CLINICAL PRACTICE…….....……38-46

Changsheng He, Jian Liu, Linhai Xu, Fanhua Sun, Yan Wang, Jia Lou.
THE RELATIONSHIP BETWEEN SERUM INFLAMMATORY CYTOKINES AND HYPERLIPIDEMIC ACUTE PANCREATITIS…..47-49

Artemov O.V, Lytvynenko M.V, Chumachenko I.V, Bondarenko A.V, Dotsenko N.V, Ostapchuk K.V, Koshelnyk O.L, Gargin V.V.
THE INFLUENCE OF THE DEMODEX MITE ON THE MORPHOLOGICAL PICTURE OF EYELID PAPILLOMA…….....……50-54

Othman K.M. Al-Sawaf, Mahmoud AM Fakhri.
CHARACTERIZATION OF SERUM SERINE PROTEASE BIOCHEMICAL PROFILE IN PATIENTS WITH RENAL FAILURE…..…..55-58

Sergey Lee, Marat Assimov, Yuriy Ignatiev, Fatima Bagiyarova, Gulbanu Absatarova, Aizhan Kudaibergenova, Sholpan Mardanova, Tatyana Tsapenko, Baimakhan Tanabayev, Assel Ibrayeva, Anel Ibrayeva, Ildar Fakhradiyev.
PREVALENCE AND FACTORS OF PROFESSIONAL BURNOUT AMONG PRIMARY HEALTHCARE WORKERS IN THE REPUBLIC OF KAZAKHSTAN: RESULTS OF A NATIONAL STUDY…….....……59-68

I.A. Yusubov.
RESULTS OF PERCUTANEOUS TREATMENT OF LIMITED FLUID FORMATIONS AFTER ABDOMINAL SURGERY…...……69-74

Nawar M. Abd-alaziz, Ammar L. Hussein, Mohammed M Abdul-Aziz.
STUDY THE RELATIONSHIP BETWEEN OSTEOPROTEGERIN AND KIDNEY INJURY MOLECULE-1 AND SOME BIOCHEMICAL VARIABLES IN PATIENTS WITH KIDNEY STONES…….....……75-78

Tsisana Giorgadze, Tinatin Gognadze.
SUBSTRATE SPECIFICITY OF β-GLUCOSIDASE FROM *YUCCA GLORIOSA* LEAVES…….....……79-82

Sheishenov Zhalil, Kemelbekov Kanatzhan, Joshibaev Seitkhan, Turtabaev Baglan, Zhunissov Bakhytzhan.
COMPARATIVE ANALYSIS OF THE CLINICAL RESULTS OF PATIENTS WITH ASD OPERATED VIA RIGHT ANTERIOR MINITHORACOTOMY AND MEDIAN STERNOTOMY…….....……83-88

Sosonna L, Ohurtsov O, Piriatinska N, Vdovitchenko V, Seleznova R, Kolba O, Gryzodub D, Rozhkova O, Shevtsov O.
INDIVIDUAL ANATOMICAL VARIABILITY OF THE SKULL`S FACIAL SECTION CONSIDERING GENDER AND CRANIOTYPE BASED ON COMPUTED TOMOGRAPHY DATA…….....……89-95

Osminina M.K, Aslamazova A.E, Podchernyaeva N.S, Khachatryan L.G, Velikoretskaya M.D, Chebysheva S.N, Polyanskaya A.V.
SYSTEMIC OR LIMITED IS HEMISCLERODERMA OF FACE IN A PERSON WITH UVEITIS? EXPERIENCE OF 10 CASES OF UVEITIS IN HEMISCLERODERMA OF FACE FROM ONE RHEUMATOLOGY CENTER…….....……96-100

F.T. Khalilova, A.A. Kerimov.
CLINICAL AND LABORATORY CHARACTERISTICS OF THE LATENT FORM OF POLYCYTHEMIA VERA……..……101-105

Ahlam S. Ibrahim, Sukayna H. Rashed.
ISOLATION AND PURIFICATION OF TRANSGLUTAMINASE 1 USING BIOCHEMICAL TECHNIQUES……...……106-111

Tingting Li, Xu Zhang, Baohong Xue, Lianping He, Qiaoqiao Chen, Dexun Zhao.
THE RELATIONSHIP BETWEEN MENTAL HEALTH AND PHYSICAL ACTIVITY AMONG STUDENTS FROM A PRIVATE UNIVERSITY: A CROSS-SECTION STUDY……112-117

Narkhojayev Nurgali, Turmetov Ibadulla, Kemelbekov Kanatzhan, Bektayev Erkebai, Akhmetov Almasbek, Zhunissov Bakhytzhan.
RESULTS OF SURGICAL TREATMENT OF PECTUS EXCAVATUM IN CHILDREN AND ADOLESCENTS……...……118-122

Krushelnytska HL, Batryn OV, Ryzhenko LM, Lytvyn NA, Dobrianska NV, Lyga AI.
INFORMATION FACTORS OF MEDIA INFLUENCE ON THE FORMATION OF STATE POLICY IN THE FIELD OF LEGAL REGULATION OF BIOMEDICAL TECHNOLOGIES……123-129

Vahe Ashot Ter-Minasyan.
EVALUATION OF KNOWLEDGE AND ATTITUDE REGARDING CERVICAL CANCER SCREENING PRACTICE: A MULTICENTER REGIONAL STUDY……130-136

Muhsin S.G. Almozie'l, Abbas A. Khudhair, Falah Hassan Shari.
REMEDIAL INTERVENTION OF FERTILITY AGENT AND GENE 35 ON INDUCED CYSTIC OVARY IN RATS……137-141

Rongzheng Yuan, Hui Wang, Jing Chen.
THE EFFECT OF LOW MOLECULAR WEIGHT HEPARIN SODIUM IN THE TREATMENT OF ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE COMORBID WITH PULMONARY HEART DISEASE ON PROMOTING THE BALANCE OF BLOOD VESSELS……142-146

Arailym Maikenova, Alexander Nersesov, Elmira Kuantay, Mukhtar Kulimbet, Massimo Giuseppe Colombo, Chavdar Pavlov, Yerkezhan Yerlanova.
EVALUATION OF PREDICTORS OF INEFFECTIVENESS OF ANTIVIRAL THERAPY FOR CHRONIC HEPATITIS C IN THE REPUBLIC OF KAZAKHSTAN: A MATCHED CASE-CONTROL STUDY……147-154

Ahmed N. Ali, Muna A. Kashmoola.
EVALUATION OF PROTEIN C AND S IN β-THALASSEMIA MAJOR……155-160

Sh.Tsiklauri, N.Nakudashvili, M.Lomaia.
EFFECT OF INTRANASAL ELECTROPHORESIS WITH 5% POTASSIUM IODATE SOLUTION ON CLINICAL OUTCOME OF PATIENTS WITH HYPERTROPHIC RHINITIS……161-164

Fang Xu, Zhijuan Xu, Ming Li.
INTRAVITREAL INJECTION CONBERCEPT IMPROVES THE BEST-CORRECTED VISUAL ACUITY IN PATIENTS WITH WET AGE-RELATED MACULAR EDEMA……165-167

Lilit Darbinyan, Margarita Danielyan, Vergine Chavushyan, Karen Simonyan, Michael Babakhanyan, Lilia Hambardzumyan, Larisa Manukyan, Kristine Karapetyan, Lusya Hovhannisyan.
THE PROTECTIVE EFFECTS OF SELENIUM-ENRICHED HYDROPONIC RADISH ON PARACETAMOL-INDUCED LIVER DAMAGE IN RATS……168-172

Grygorova A.O, Grygorov S.M, Yaroslavska Yu.Yu, Mykhailenko N.M, Demyanyk D.S, Steblianko A.O, Rak O.V, Voloshan O.O, Nazaryan R.S.
SIGNS OF ORAL CAVITY MICROCIRCULATORY DISORDERS IN ADOLESCENTS WHO SMOKE……173-177

Ali H. Kadhim, Nihad N. Hilal, Taghreed AH. Nassir.
A COMPARATIVE STUDY ON THE VARIABLE EFFECTS OF ALCOHOL AND NON-ALCOHOL-RELATED FATTY LIVER DISEASE ON METABOLIC AND INFLAMMATORY BIOMARKERS……178-182

Papoyan Varduhi, Galstyan Alina, Sargsyan Diana.
FACTOR ANALYSIS OF THE COMPETENCIES OF PERSONAL RESOURCES OF SPECIALIST……183-189

Chulpanov Utkir, Turdaliyeva Botagoz, Buleshov Myrzatai, Zhanabaev Nurlan, Kanatzhan Kemelbekov.
COMPARATIVE EVALUATION OF THE EFFECTIVENESS OF INNOVATIVE HIGH-TECH CARDIAC SURGERY IN PATIENTS WHO HAVE SUFFERED AN ACUTE MYOCARDIAL INFARCTION……190-195

Tea Charkviani, Jenara Kristasashvili, Tamar Barbakadze, Mariam Gabadze, Tamar Kbilashvili, Mariam Makharadze.
THE RELATIONSHIP BETWEEN FOLLICLE SIZE, OOCYTE MATURATION, BLASTOCYST FORMATION, BLASTOCYST PLOIDY, AND PREGNANCY OUTCOMES IN YOUNG WOMEN UNDERGOING IVF……196-203

Yunfei Wu, Koulong Wu, TianhuaDu.
STUDY ON THE EFFECTS OF ART PAINTING COMBINED WITH SPORTS ON MYOPIA PREVENTION AND VISION IMPROVEMENT……204-207

Lulëjeta Ferizi-Shabani, Shefqet Mrasori, Valbona Ferizi, Gonxhe Barku, Milazim Gjocaj, Blerim Krasniqi, Basri Lenjani.
EVALUATION OF DENTAL AND PERIODONTAL STATUS IN CHILDREN WITH TYPE 1 DIABETES MELLITUS……208-212

Rana Dawood Salman Al-kamil, Mustafa Ragheb Abed, Sanaryh Mohammed Al-awad, H. N. K. AL-Salman, Hussein H. Hussein, Dawood Chaloob Hilyail, Falah Hassan Shari.
ISOLATION, CHARACTERIZATION, AND ANTIHYPERTENSIVE ACTIVITY ALKALOIDS EXTRACTED FROM THE LEAVES OF THE ALSTONIA SCHOLARIS PLANT……213-217

Tchernev G, Broshtilova V, Kordeva S.
SHARK PEDICLE ISLAND FLAP FOR BASAL CELL CARCINOMA OF THE PERIALAR ZONE OF THE NOSE: PHOTOXICITY AND PHOTOCARCINOGENICITY MEDIATED BY POTENTIALLY NITROSAMINE CONTAMINATED DRUG INTAKE -A NEW EXPLANATION FOR THE SKIN CANCERS PATHOGENESIS? ……218-222

Meruert T. Orazgalieva, Meyrbek J. Aimagambetov, Zhanna D. Bryzhakhina, Serik D. Zhanybekov, Ainash S. Orazalina.
RISK FACTORS FOR THE DEVELOPMENT OF COAGULOPATHY DURING SURGERY IN MECHANICAL JAUNDICE.....223-228

Noor N. Noori, Nawal A. Murtadha.
UNCONTROLLED TYPE 2 DIABETES MELLITUS MODULATED PLASMA LEVELS OF LIPID CATABOLIC PROTEINS….....229-233

Ling-Ling Zhou, Zhou-Zhou Lin, Lian-Ping He.
PREVALENCE OF DEPRESSION AMONG UNIVERSITY STUDENTS IN CHINA: A PROTOCOL FOR A SYSTEMATIC REVIEW AND META-ANALYSIS…….....……234-236

Nadine Khayyat, Sima Kalaldeh, Suha Khalifa.
OPTIMISING THE CLINICAL ASSESSMENT OF CHILDHOOD AND ADOLESCENT OBESITY IN JORDAN……..……237-241

Shuasheva Y.A, Buleshov M.A, Kemelbekov K.S.
CLINICAL, IMMUNOLOGICAL AND THESIOGRAPHIC CHARACTERISTICS RHEUMA-TOID ARTHRITIS AND CHRONIC RHEUMATICHEARTDISEASE…….....……242-248

Sana A. Abdulmawjood, Eman S. Mahmoud, Rana T Altaee.
ASSESSMENT OF CIPROFLOXACIN EFFECTS ON SOME CHICKS' ORGANS: A COMPREHENSIVE BIOCHEMICAL AND HISTOLOGICALSTUDY…….....……249-254

Knarik V. Kazaryan, Naira G. Hunanyan, Margarita H. Danielyan, Rosa G. Chibukchyan, Yulia Y. Trofimova, Arus V. Mkrtchyan, Kristine V. Karapetyan, Karwan H. Syan, Tatevik A. Piliposyan.
REGULATION OF SPONTANEOUS ELECTRICAL ACTIVITY IN THE ORGANS OF RE-PRODUCTIVE SYSTEM BY OXYTOCIN…….....……255-259

Lantukh I.V, Kucheriavchenko V.V, Yurko K.V, Bondarenko A.V, Merkulova N.F, Mohylenets O.I, Gradil G.I, Bondar O.Ye, Bodnia I.P, Burma Ya.I, Tsyko O.V, Tkachenko V.G.
PSYCHOLOGICAL FEATURES OF REHABILITATION OF HIV-INFECTED PATIENTS…….....……..260-264

Serikbayeva Saltanat, Shaimerdenova Gulbanu, Ormanov Namazbai, Ormanov Talgat, Abuova Gulzhan, Kaishibayeva Gulnaz, Kemelbekov Kanatzhan.
PEROXIDATION OF SALIVA LIPIDS IN PATIENTS WITH POSTCOVID SYNDROME DURING HIRUDOTHERAPY…...……265-269

M.V. Poghosyan, H.Y. Stepanyan, Avetisyan Z.A, J.S. Sarkissian.
THE EFFECTS OF HYDROCORTISONE ON SYNAPTIC PROCESSES IN PARKINSON'S DISEASE UNDERLYING THE POTENTIAL THERAPEUTICSTRATEGIES…….....…….270-277

Changsheng He, Jian Liu, Linhai Xu, Fanhua Sun.
THE EFFECT OF PERCUTANEOUS CATHETER DRAINAGE COMBINED WITH SOMATOSTATIN ON INFLAMMATION AND PLASMA THROMBOXANE 2, PROSTACYCLIN I2 LEVELS IN PATIENTS WITH SEVERE PANCREATITIS…….....…….278-283

Tea Chitadze, Nino Sharashidze, Tamar Rukhadze, Nino Lomia, Giorgi Saatashvili.
EVALUATION OF LEFT VENTRICULAR SYSTOLIC FUNCTION IN POSTMENOPAUSAL WOMEN WITH BREAST CANCER RECEIVING ADJUVANT ANTHRACYCLINE AND TRASTUZUMAB THERAPY: A 2-YEAR FOLLOW-UP STUDY…….....……284-293

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THE RELATIONSHIP BETWEEN FOLLICLE SIZE, OOCYTE MATURATION, BLASTOCYST FORMATION, BLASTOCYST PLOIDY, AND PREGNANCY OUTCOMES IN YOUNG WOMEN UNDERGOING IVF

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Abstract.

Introduction: The relationship between follicle size, oocyte quality, and blastocyst ploidy is not fully established. This question becomes especially important for poor responders and older reproductive age women, where optimal follicle size and oocyte quantity cannot always be achieved during ovarian stimulation.

The aim of this study is to determine the relationship between follicle size, oocyte maturation, blastocyst formation, blastocyst ploidy, and pregnancy outcomes in young women undergoing in vitro fertilization (IVF).

Materials and Methods: The study involved 32 oocyte donors aged 19 to 35. For ovarian stimulation, a protocol with GnRH-antagonists was used, employing downregulation with oral contraceptives. The ovulation trigger was administered when 20% of follicles reached 18 mm. Aspiration was performed 35 hours after the ovulation trigger was administered. Follicle size was measured immediately before the aspiration needle was inserted and follicle fluid was aspirated; data (follicle size and oocyte from this follicle) were recorded individually by the embryologist. The resulting blastocysts underwent preimplantation genetic testing for aneuploidy (PGT-A) using NGS. Pregnancy outcomes were assessed by biochemical indicators, miscarriages, and live births.

Results: Out of 555 measured follicles, 508 oocytes were obtained (91.5%). The number of mature oocytes (MII) was 411 (80.9%), and there were 97 immature oocytes (19.2%). Out of the 97 immature oocytes, 51 were germinal vesicle (GV) oocytes (10.04%), and 46 (9.06%) were MI oocytes without a polar body. Follicles were divided into four groups based on size: Group I — <15 mm, Group II — 15-18 mm, Group III — 18-20 mm, Group IV — >20 mm. There were significantly more mature oocytes in the second, third, and fourth groups compared to the first, indicating that follicle size has a substantial impact on retrieving MII oocytes ($p<0.0001$). Especially high number of mature oocytes were observed in the second and third groups.

Fertilization and blastocyst formation from oocytes obtained from larger follicles were higher than from smaller follicles ($p<0.0001$). The frequency of obtaining euploid blastocysts did not significantly differ between the groups, and no significant relationship was found between follicle size and the formation of euploid blastocysts. Women who underwent genetic testing of embryos and transferred euploid embryos had significantly lower rates of biochemical pregnancy and miscarriages, as well as significantly higher live birth rates compared to those who did not undergo genetic testing of embryos.

Conclusion: Oocyte maturation, fertilization, and blastocyst formation depend on follicle size. However, follicle size is not an indicator of blastocyst euploidy. Preimplantation genetic testing for aneuploidy (PGT-A) significantly increases pregnancy success and live birth rates while reducing miscarriage rates.

Key words. Follicle size, oocyte quality, blastocyst ploidy, oocyte maturation, blastocyst formation, in vitro fertilization (IVF), preimplantation genetic testing for aneuploidy (PGT-A), ovarian stimulation, euploid blastocysts, pregnancy outcomes, GnRH-antagonists protocol, oocyte donors, live birth rates, miscarriage rates.

Introduction.

Assisted reproductive technologies (ARTs) have become a routine part of women's reproductive health care. As the field advances, enhancing its effectiveness remains a key focus. The success of treatment depends on various factors, including egg quality associated with the woman's age [1-3], controlled ovarian stimulation (COS) protocols [4,5], the type of ovulation trigger administered for final oocyte maturation, blastocyst quality and ploidy [6,7], endometrial condition, synchronization between the endometrium and embryo during implantation, and overall health status of the woman [8,9].

Over the last decade, there has been an increased demand for egg freezing among young women for social and medical reasons [10]. A critical point is that not all mature eggs are capable of fertilization and may not develop to the blastocyst stage [11]. Determining blastocyst ploidy using preimplantation genetic testing (PGT-A) significantly improves pregnancy rates, reduces implantation failures and miscarriage rates, and increases live birth rates [12,13].

Developing an ideal ovarian stimulation protocol and achieving the optimal number of eggs for a successful pregnancy, as well as identifying the ideal follicle size from which genetically complete embryos are derived, remains a significant challenge [14,15]. This issue is particularly critical for poor responders and patients planning to delay pregnancy until late reproductive age [16,17].

It is known that larger follicles yield mature oocytes with a higher potential for blastocyst formation [14,15]. However, in poor responders and older women, obtaining a sufficient number of large follicles is often not possible; therefore, achieving fully developed oocytes from relatively smaller follicles becomes relevant [16]. Several studies have explored potential correlations between follicle size and oocyte maturity, blastocyst formation, and ploidy, but such studies are few and have not yielded conclusive results [11,16].

Establishing the relationship between follicle size and embryo ploidy is of great practical value, allowing clinicians to improve follicle selection criteria and refine ovarian stimulation protocols to better select follicle sizes more likely to result in euploid blastocysts [18]. This, in turn, increases the chances of achieving pregnancy and live birth [19]. Therefore, the aim of our study was to determine the relationship between follicle size, oocyte maturation, blastocyst formation, blastocyst ploidy, and pregnancy outcomes in young women undergoing in vitro fertilization.

Materials and Methods.

The study was conducted at the Georgian-American Reproductive Clinic "ReproART" in Tbilisi, Georgia, between 2019 and 2022. It involved 32 anonymous oocyte donors aged 19 to 35. Each donor was associated with a potential parent. Before the start of ovarian stimulation, all participating donors were informed about the nature of the study. They were made aware that measuring each follicle prior to aspiration could prolong anesthesia. Only donors who expressed willingness and signed informed consent were included in the study.

The criteria for participation were consistent for all women. These criteria are detailed in Table 1.

Table 1. *The criteria for participation were consistent for all women.*

Egg Donor criteria	Average Indicator
Age	25.0 ± 3.5
AMH (ng/mL)	4.2 ± 2.0
Antral follicle count (AFC)	24.7 ± 7.6
BMI	21.9± 2.4
Follicle stimulated hormone basal level (mIU/mL)	7.8 ± 2.1
TSH (mIU/mL)	2.2± 1.3
PRL (ng/mL)	16.3 ± 5.7
Sperm parameters	normozoospermia
Sperm DNA fragmentation (%)	<15

Participants were excluded from the study if they had the following conditions: irregular menstrual cycles, abnormal BMI, polycystic ovary syndrome, sexually transmitted diseases, complicated obstetric history, endometriosis, uterine abnormalities, previous ovarian surgeries, or infertility due to male factors.

The ovarian stimulation protocol was identical for all donors. A GnRH-antagonist protocol with prior ovarian downregulation was employed using oral contraceptives to synchronize donor and recipient cycles. Each donor received recombinant FSH (Gonal-F, Merck Serono, Germany) combined with highly purified human menopausal gonadotropin (h-hMG Menopur, Ferring Pharmaceuticals, Switzerland).

Stimulation began on the fifth day after stopping oral contraceptives. The initial medication dose was a double-high dose of gonadotropins at 450 IU FSH for the first two days, followed by a reduced dose. The duration of stimulation depended on follicular growth rate, averaging 11-12 days.

The first follicular monitoring was conducted on the fifth or sixth day of stimulation, with subsequent monitoring every other day or daily as needed. Monitoring comprised ultrasound assessment of follicles (The GE Voluson E8- GE HealthCare US) and hormonal evaluations (FSH, LH, E2).

Hormonal monitoring parameters are detailed in Table 2. Medication dosing was adjusted based on follicular response. The GnRH-antagonist (Cetrotide 0.25 mg, Merck Serono, Darmstadt, Germany) was administered when one follicle reached 14 mm in diameter. Ovulation triggers included 10,000 IU of chorionic gonadotropin (Pregnyl 5000 IU, Organon, Netherlands) alone, a combination of 1,500 IU chorionic gonadotropin and GnRH-agonist (Decapeptyl 0.2 mg, Ferring Pharmaceuticals, Switzerland), or GnRH-agonist alone (Decapeptyl 0.2 mg).

Table 2. *Details of Hormonal monitoring parameters.*

Parameters	Mean value*
FSH[1] level at DR (mIU/mL)	3,6± 2,5
E2[2]level at DR[3] (pg/mL)	10.4 ± 8.6
Total gonadotropins administration (IU)[4]	3203±536
Days of stimulation	10,5 ± 2,1
E2 level on day of trigger (pg/mL)	7325±1567
Follicle diameter at retrieval (mm)	18,4±1.7
Total number of retrieved oocytes	19,3±5.5

[1]FSH – follicle stimulating hormone
[2]E2 -estradiol
[3]DR -downregulation
[4]Total gonadotropins – total amount of FSH dose (either r-FSH or hMG)
**Mean value ± standard deviation (N)*

Aspiration was performed 35 hours after administering the ovulation trigger. For donors with more than 25 follicles, only the GnRH-agonist (Decapeptyl 0,2 mg, Ferring Pharmaceuticals, Switzerland) was used to prevent ovarian hyperstimulation.

Donors underwent ovarian follicle aspiration in the dorsal lithotomy position under general anesthesia (IV anesthesia with spontaneous breathing maintenance). Follicle aspiration was performed transvaginally under ultrasound guidance using 17-gauge aspiration needles (single lumen needles, Gynetics-Fertitech, Belgium). Aspiration was conducted at a pressure of 120 mmHg. Each follicle was measured in two dimensions before puncture and aspiration, and the average data were recorded. It was also noted whether an oocyte was retrieved from the measured follicle. The embryologist recorded the follicle size and the retrieved oocytes. If two oocytes were found in the test tube, or if the oocyte was from an unmeasured follicle, it was excluded from the study.

All oocytes underwent the ICSI procedure. Fertilization assessment—identifying one or two pronuclei (PN)—was conducted 16 to 18 hours post-ICSI. For embryo culture, Quinn's Advantage Fertilization medium (ref no.: ART-1020, Origio, Netherlands) was used. After fertilization assessment, embryos were transferred to Quinn's Advantage Cleavage (ref no.: ART-1026, Origio, Netherlands) in individual droplets. On day three of embryo development, Zona Pellucida was disrupted using a laser (device), and the embryos were transferred to the blastocyst culture medium Quinn's Advantage Protein Plus Blastocyst Medium (ref no.: ART-1529, Origio, Netherlands) in individual droplets. Embryo evaluation was performed at

the blastocyst stage on days five, six, and seven. Blastocyst morphological quality was assessed using the Gardner grading method. High-quality blastocysts (AA to BC; CB) underwent trophectoderm biopsy—using vitrification—and 5-8 cells from the biopsied trophectoderm were sent to the genetic laboratory for ploidy analysis (PGT-A). Genetic testing was conducted at Reprogenetics/Cooper Genomics (New Jersey, USA, or UK) for comprehensive chromosomal analysis by next-generation sequencing (NGS)

Results and Discussion.

From the 555 measured follicles from 32 donors, 508 oocytes were obtained (91.5%). The number of mature oocytes (MII) was 411 (80.9%), 97 immature oocytes (19.2%), including 51 germinal vesicle (GV) oocytes (10.04%) and 46 oocytes without a polar body (MI) (9.06%). Follicles were divided into four research groups: Group 1 (<15 mm); Group 2 (15-18 mm); Group 3 (18-20 mm); Group 4 (>20 mm).

All statistical analyses and visualizations in this presentation were performed using T-test, ANOVA, Python to determine the significance of differences between groups.

Follicle Size and Oocyte Maturity:

In the first research group (<15 mm), of the 113 oocytes obtained, 51 (45.13%) were GV; 28 (24.78%) were MI; and 34 (30.09%) were MII. It was noted that only GV quality oocytes were obtained from follicles smaller than 10 mm.

In the second group (15-18 mm), 191 oocytes were collected, resulting in 27 GV (14.14%), 16 MI (8.38%), and 148 MII (77.49%).

In the third group (18-20 mm), no GV oocytes were founded; of the 99 oocytes, 86 were MII (86.87%) and 13 were MI (13.13%).

In the fourth group (>20 mm), all 128 oocytes were mature MII (100%).

Statistical analysis shows a clear increase in the frequency of oocyte maturity parallel to follicle size. Notably, significant differences were observed in the second and third groups.

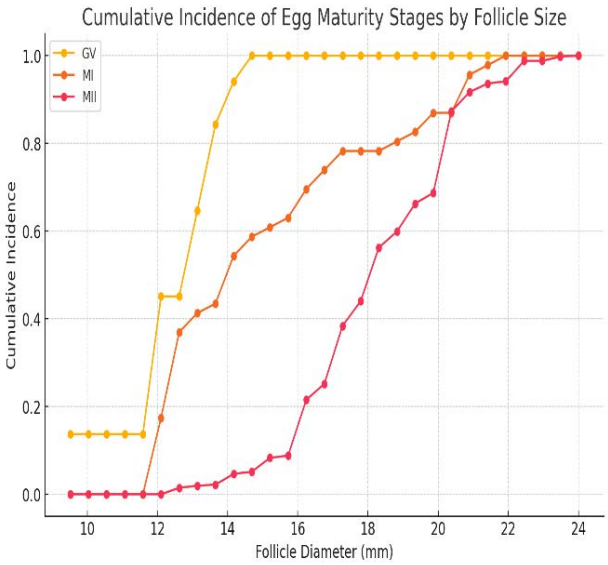

Figure 1. *The cumulative incidence plot illustrates the relationship between follicle size and the stages of egg maturity (GV, MI, MII).*

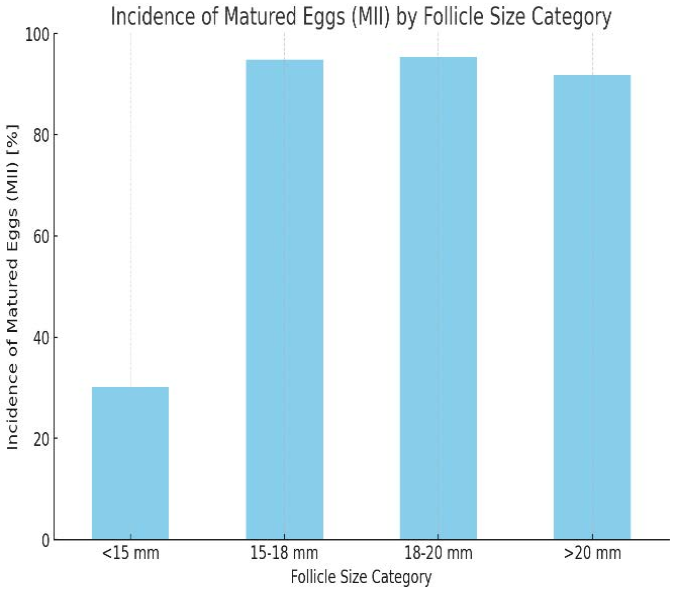

Figure 2. *A graphical representation of the relationship between oocyte maturity and follicle size is clearly evident.*

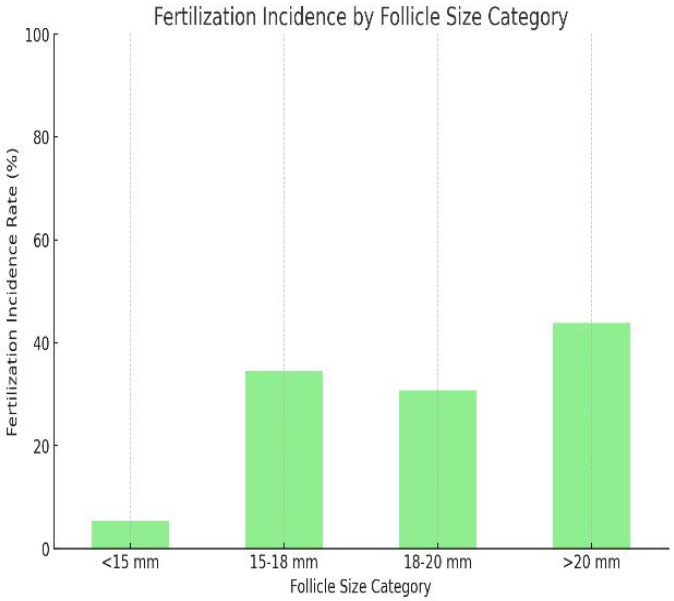

Figure 3. *The frequency of fertilization relative to follicle size.*

The cumulative incidence plot (Figure 1) illustrates the relationship between follicle size and the stages of egg maturity (GV, MI, MII). It shows that as follicle diameter increases, the likelihood of reaching the MII stage also increases, while smaller follicles tend to remain at the GV stage.

A graphical representation (Figure 2) is provided here, showing the categorization of follicle sizes into groups, where the relationship between oocyte maturity and follicle size is clearly evident.

This bar chart illustrates the incidence of matured eggs (MII) categorized by follicle size ranges. The data is divided into four categories: <15 mm, 15-18 mm, 18-20 mm, and >20 mm. The chart indicates that the incidence of matured eggs is highest in the 15-18 mm and 18-20 mm categories, with rates of 94.85% and 95.38%, respectively. In contrast, follicles smaller than 15

mm have a significantly lower incidence rate of matured eggs at 30.09%, and follicles larger than 20 mm at 91.78%.

In some studies, the size of the follicle at the time of retrieval has long been considered a significant factor in predicting oocyte maturity. Larger follicles are typically associated with a higher likelihood of retrieving mature oocytes (MII stage). This is supported by previous studies that suggest a positive correlation between follicle size and oocyte maturation rates [15]. The underlying physiology indicates that larger follicles have undergone more advanced stages of development, thereby completing the necessary processes for meiotic progression. A study by Weissman et al. (2007) also highlighted that follicles above 18 mm are more likely to yield mature oocytes, which is crucial for successful fertilization [1]. Other authors noted that follicle size alone is not a definitive predictor of oocyte quality or embryo viability, as other factors, such as cytoplasmic maturity and the in vitro culture environment, play critical roles [16].

Out of the 411 mature oocytes obtained, 347 were fertilized (84.4%), and of the 46 MI oocytes, 16 were fertilized. The frequency of fertilization relative to follicle size is shown in Figure 3.

The relationship between follicle size and the likelihood of fertilization (indicated by the presence of two pronuclei, 2PN) was investigated. This analysis aimed to determine whether follicle size could predict the incidence of mature eggs (MII) and their subsequent fertilization.

The t-test results show no statistically significant difference between the follicle sizes of fertilized and mature oocytes ($P = 0.2741$; $Z = 0.20$). The analysis suggests that follicle size is not a significant predictor of fertilization (2PN). The observed differences in follicle sizes between fertilized and mature oocytes are not statistically significant, as indicated by the p-value (0.2741) and Z-value (0.20). Additionally, the ROC curve analysis was inconclusive due to the lack of negative samples, which necessitates further research in the future.

This comprehensive analysis supports the conclusion that follicle size does not significantly influence the likelihood of oocyte fertilization, providing valuable insights for clinical decision-making and research in reproductive medicine.

While larger follicles tend to yield more mature oocytes, our data showed no significant difference in fertilization rates per mature oocyte across different follicle sizes. This finding aligns with existing literature, suggesting that once oocytes reach maturity, their fertilization potential is more influenced by intrinsic oocyte quality and sperm factors rather than the follicle size [14]. A study by Dubey et al. (1995) found that while there was a positive correlation between follicle size and the maturity of oocytes, follicle size alone was not a reliable predictor of successful fertilization [11].

Follicle Size and Blastocyst Formation:

No significant differences were observed in the quality of blastocysts formed from oocytes based on the size of their originating follicles.

Correlation analysis, ANOVA, and t-tests were employed to assess the relationship between follicle size and blastocyst grade (Figure 4). These statistical methods collectively provided a robust evaluation, revealing a statistically significant but modest

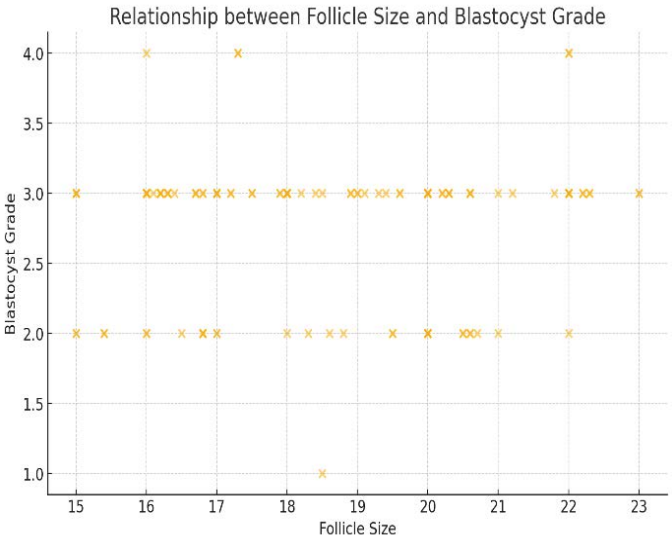

Figure 4. *Correlation analysis, ANOVA, and t-tests were employed to assess the relationship between follicle size and blastocyst grade.*

effect of follicle size on blastocyst formation, suggesting that other factors also play a significant role.

The positive coefficient for follicle size (0.0400) suggests a positive relationship between follicle size and blastocyst grade. The p-value (<0.001) is highly significant, confirming the relationship is not due to random chance. factors also play a significant role. Further research is needed to identify additional factors that influence blastocyst grade. The R-squared value is relatively low, shows that while the relationship is statistically significant, follicle size alone does not explain much of the variance in blastocyst grade.

Our analysis revealed a nuanced relationship between follicle size and blastocyst formation. Although larger follicles are generally associated with higher oocyte maturity rates, which is a critical factor for successful fertilization and subsequent embryo development [21], the conversion rate to blastocysts did not increase proportionally. This discrepancy may be attributed to factors beyond follicle size, such as oocyte cytoplasmic maturation and in vitro culture conditions [22]. These findings suggest that while follicle size is a useful marker for predicting oocyte yield, it is less reliable for forecasting blastocyst development.

Follicle Size and Blastocyst Euploidy:

Out of 374 fertilized oocytes, preimplantation genetic testing (PGT-A) of 145 resulting blastocysts showed that 76 were euploid (52.41%). The average follicle size from which the oocytes forming euploid blastocysts were obtained was 18.68±2.12 mm. The analysis indicated no statistical difference in the average size of follicles that formed aneuploid blastocysts, which was 18.65±2.13 mm. An interesting observation was that none of the mature oocytes from the first group (<15 mm) developed into blastocysts.

ROC and AUC Analysis:

The AUC of 0.65 suggests that follicle size has a poor predictive power for determining euploid blastocyst formation.

The significant Z-value and very low p-value provide strong

evidence of a relationship between follicle size and the likelihood of obtaining a euploid blastocyst (Figure 5).

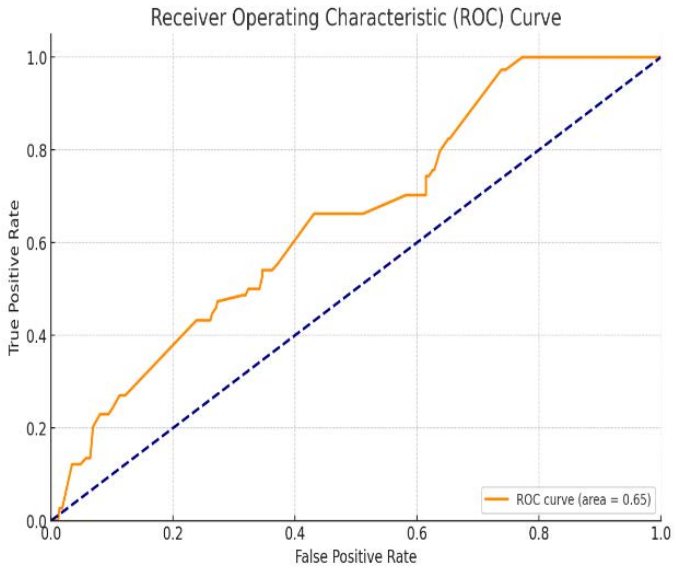

Figure 5. *The significant Z-value and very low p-value provide strong evidence of a relationship between follicle size and the likelihood of obtaining a euploid blastocyst.*

The analysis shows that while there is a high rate of euploid blastocysts from mature oocytes, follicle size alone does not significantly predict euploidy. Other factors, such as the incubation environment, cultivation mediums and also play a crucial role in determining euploid blastocyst likelihood.

Determining the relationship between follicle diameter, from which mature MII oocytes are obtained, and blastocyst euploidy is important for clinicians. Establishing this relationship as a predictive factor is especially crucial for patients who freeze oocytes indefinitely for later reproductive age, essentially doing so blindly.

Extended culture to the blastocyst stage, coupled with preimplantation genetic testing for aneuploidy (PGT-A), has become a standard practice to enhance embryo selection. This approach allows for the identification and transfer of euploid embryos, which are more likely to result in successful pregnancies. Studies have consistently shown that the use of PGT-A significantly improves implantation rates and reduces miscarriage rates by ensuring that only chromosomally normal embryos are selected for transfer [17]. A large-scale study by Sadecki et al. (2021) demonstrated that PGT-A improves live birth rates by reducing the risk of transferring aneuploid embryos [19].

Pregnancy Outcomes:

A retrospective analysis was conducted on the outcomes of pregnancies resulting from the transfer of genetically tested and non-tested embryos.

Embryo transfer was performed after endometrial medical preparation in recipients. Endometrial preparation began either after taking oral contraceptives (prescribed only to surrogate mothers to suppress ovarian fuction) or directly on the second day of the menstrual cycle. To prepare the endometrium, recipients received 9 mg of estradiol per day (Femostone 2/10 – Abbot, Netherlands). To further suppress their own ovulation, surrogate mothers were additionally given a GnRH-agonist injection until progesterone was prescribed. The average preparation duration was 10-15 days, depending on endometrial thickness. Progesterone (Luteina 200 mg - Poland) for vaginal and i/m use (Prolutex 25 mg – IBSA Switzerland) was prescribed once the endometrial thickness exceeded 8 mm. On this day, estradiol and progesterone levels were measured in the blood, and embryo transfer was scheduled if the blood progesterone level was < 1 ng/ml. The embryo transfer was performed on the sixth day after starting progesterone.

A total of 110 genetically tested embryo transfers resulted in 48 pregnancies (43.63%), whereas 63 transfers with non-tested embryos resulted in 23 pregnancies (36.5%). Miscarriages in the PGT-A group were 12.5% (6/48) compared to 20.6% (6/23) in the non-PGT-A group (Figure 6).

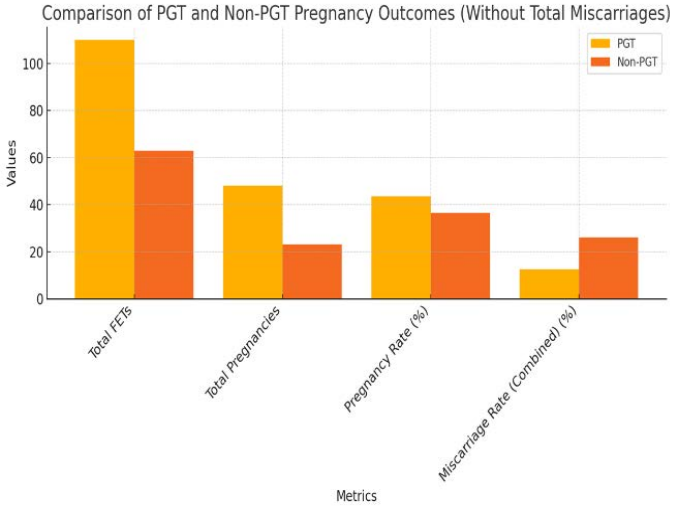

Figure 6. *Miscarriages in the PGT-A group were 12.5% (6/48) compared to 20.6% (6/23) in the non-PGT-A group.*

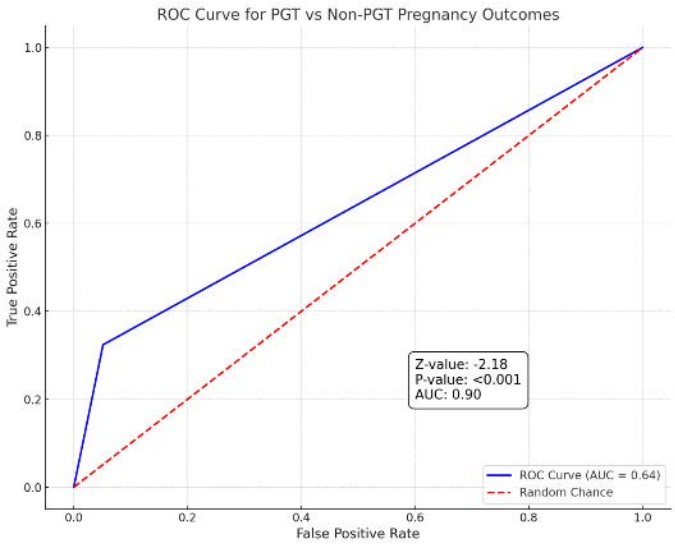

Figure 7. *The logistic regression analysis revealed a statistically significant difference between the PGT and non-PGT groups (p < 0.001).*

To rigorously test whether the difference in pregnancy rates between the PGT and non-PGT groups is statistically significant, accounting for the number of patients in each group. The logistic regression analysis (Figure 7) revealed a statistically significant difference between the PGT and non-PGT groups ($p < 0.001$). The Z-value (-2.18) confirmed the distinct outcomes in the PGT group after adjusting for group size. The ROC curve demonstrated the model's strong predictive accuracy, with an AUC of 0.90, highlighting its effectiveness in distinguishing between the two groups regarding pregnancy outcomes.

Numerous studies have compared the efficacy of PGT-A with non-PGT-A embryo transfers, with mixed results depending on the patient population and study design.

PGT-A is associated with higher implantation and clinical pregnancy rates, particularly in older women and those with recurrent pregnancy loss. For instance, a clinical pregnancy rate is approximately 60% after PGT-A, significantly higher than non-PGT-A transfers [13]. Similarly, Scott et al. demonstrated that PGT-A cycles led to an increased implantation rate of around 65%, highlighting the technique's potential to improve pregnancy outcomes in select populations [18].

One of the primary benefits of PGT-A is its ability to reduce miscarriage rates by selecting euploid embryos, which are less likely to result in early pregnancy loss. Dahdouh et al. found that the miscarriage rate after PGT-A was significantly lower, often below 10%, compared to non-PGT-A transfers [12].

Despite these advantages, the universal application of PGT-A remains controversial. Mastenbroek et al. found no significant difference in live birth rates between PGT-A and non-PGT-A groups in younger women, questioning the necessity of PGT-A in populations with a good prognosis [23], The study suggests that PGT-A should be applied selectively rather than routinely.

Overall, PGT-A has shown substantial benefits in improving pregnancy outcomes, particularly in older women and those with a history of pregnancy loss. However, its application should be tailored to the individual patient's characteristics and clinical history to maximize the chances of a successful pregnancy. Further large-scale studies are needed to refine the indications for PGT-A and confirm its long-term benefits in diverse patient populations.

Conclusion.

Oocyte maturation, fertilization, and blastocyst formation depend on follicle size. However, follicle size is not an indicator of blastocyst euploidy. Preimplantation genetic testing for euploidy (PGT-A) significantly increases pregnancy and live birth rates while reducing the frequency of miscarriages.

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Взаимосвязь между размером фолликула, созреванием ооцита, образованием бластоцистов, плоидностью бластоцистов и исходами беременности у молодых женщин, проходящих процедуру ЭКО

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Абстракт

Связь между размером фолликула, качеством ооцитов и плоидностью бластоцистов до конца не установлена. Этот вопрос приобретает особую важность для пациенток с плохим ответом и женщин пожилого материнского или позднего репродуктивного возраста, когда оптимальный размер фолликула и оптимальное количество яйцеклеток не всегда могут быть достигнуты при медикаментозной стимуляции яичников.

Цель исследования - определить взаимосвязь между размером фолликула, созреванием ооцита, образованием бластоцистов, плоидностью бластоцистов и исходом беременности у молодых женщин, прошедших экстракорпоральное оплодотворение.

Методы и материалы

В исследовании приняли участие 32 донора яйцеклеток в возрасте от 19 до 35 лет. Для медикаментозной стимуляции яичников применяли протокол с антагонистами гонадотропин-рилизинг гормона (GnRH-antagonist) методом даунрегуляции яичников с помощью пероральных контрацептивов. Триггер овуляции назначался когда 20% фолликулов достигали размера 18 мм. Аспирацию проводили на 35-й час после назначения триггера овуляции. Размер фолликулов определяли один за другим непосредственно перед введением аспирационной иглы в фолликул и аспирацией фолликулярной жидкости. Полученные яйцеклетки и размер фолликула, из которого был получен указанный ооцит, записывал эмбриолог индивидуально. Полученные бластоцисты подвергали преимплантационному генетическому тестированию на выявление анеуплоидии (PGT-A) методом NGS. Исход беременности оценивались по биохимическим показателям беременности, выкидышей и живорождения.

Результаты

Из 555 измеренных фолликулов было получено 508 ооцитов (91,5%). Число зрелых яйцеклеток (MII) составило 411 (80,9%), незрелых яйцеклеток - 97 (19,2%), из 97 незрелых яйцеклеток 51 представляли собой ооциты зародышевых пузырьков (GV) (10,04%), 46 (9,06%) ооцита не имели полярного тельца (MI). Фолликулы были разделены на 4 исследовательские группы по размеру: I группа - <15 мм; II группа – 15-18 мм; III группа – 18-20 мм; IV группа– >20 мм. Количество зрелых ооцитов было значительно выше во второй, третьей и четвертой группах по сравнению с первой группой, что указывает на то, что размер фолликула оказывает существенное влияние на извлечение ооцитов MII ($p<0,0001$). Особенно больше зрелых ооцитов наблюдались во второй и третьей группах.

Установлено, что оплодотворение и образование бластоцистов из яйцеклеток, полученных из крупных фолликулов выше, чем у яйцеклеток, полученных из мелких фолликулов ($p < 0,0001$); Установлено, что частота получения эуплоидных бластоцистов достоверно не различалась между исследуемыми группами. Существенной взаимосвязи между размером фолликула и образованием эуплоидных бластоцист не выявлено.

Женщины, прошедшие генетическое тестирование эмбрионов и перенесшие эуплоидные эмбрионы, имели значительно более низкие показатели биохимической беременности и выкидышей, а также значительно более высокие показатели живорождения, по сравнению с теми, кто не проходил генетическое тестирование эмбрионов.

Заключение

Созревание ооцита, оплодотворение и образование бластоцистов зависят от размера фолликула. Однако размер фолликула не является показателем эуплоидии бластоцистов. Преимплантационное генетическое тестирование на эуплоидию (PGT-A) значительно увеличивает успешность беременности и частоту живорождения, одновременно снижая частоту выкидышей.

Ключевые слова: Размер фолликула, качество ооцитов, плоидия бластоцистов, созревание ооцитов, формирование бластоцистов, экстракорпоральное оплодотворение (ЭКО), преимплантационное генетическое тестирование на анеуплоидии (PGT-A), стимуляция яичников, эуплоидные бластоцисты, исходы беременности, протокол с антагонистами ГнРГ, доноры ооцитов, показатели живорождения, показатели выкидышей.

ფოლიკულის ზომის, კვერცხუჯრედის მომწიფების, ბლასტოცისტის ფორმირების, ბლასტოცისტის პლოიდიის და ორსულობის შედეგების ურთიერთკავშირი ახალგაზრდა ქალებში ინ ვიტრო განაყოფიერების პროგრამებში

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აბსტრაქტი

ფოლიკულის ზომასა და კვერცხუჯრედის ხარისხს და ბლასტოცისტის პლოიდიას შორის კავშირი ბოლომდე არ არის დადგენილი. ამ საკითხს განსაკუთრებული მნიშვნელობა აქვს ღარიბ მოპასუხე პაციენტებსა და გვიან რეპროდუქციული ასაკის ქალების შემთხვევაში, როდესაც საკვერცხეების მედიკამენტოზური სტიმულაციის დროს ყოველთვის ვერ მიიღწევა ფოლიკულის ოპტიმალური ზომა და კვერცხუჯრედების ოპტიმალური რაოდენობა.

შრომის მიზანს წარმოადგენდა ფოლიკულის ზომას, ოოციტების მომწიფებას, ბლასტოცისტების ფორმირებას, ბლასტოცისტების პლოიდიასა და ორსულობის გამოსავალს შორის ურთიერთამოკიდებულების დადგენა ახალგაზრდა ქალებში, რომლებიც იტარებენ ინ ვიტრო განაყოფიერებას

მეთოდები და მასალები

კვლევაში მიიღო მონაწილეობა 19-დან 35 წლის ასაკამდე 32-მა კვერცხუჯრედის დონორმა. საკვერცხეების მედიკამენტოზური სტიმულაციისთვის გამოყენებული იქნა GnRH-antagonist პროტოკოლი საკვერცხეების წინასწარი დათრგუნვის (downregulation) მეთოდით ორალური კონტრაცეპტივების გამოყენებით. საოვულაციო ტრიგერი ინიშნებოდა, როდესაც ფოლიკლების 20% აღწევდა 18 მმ-ს. ასპირაცია ტარდებოდა საოვულაციო ტრიგერის დანიშვნიდან 35-ე საათზე. სათითაოდ ხდებოდა ფოლიკულების ზომის განსაზღვრა უშუალოდ ფოლიკულში საასპირაციო ნემსის შესვლამდე და ასპირაციამდე. მიღებული კვერცხუჯრედები და ფოლიკულის ზომა, საიდანაც იქნა მიღებული აღიშნული კვერცხუჯრედი, ემბრიოლოგის მიერ აღირიცხებოდა ინდივიდუალურად. მიღებულ ბლასტოცისტებზე ტარდებოდა პრეიმპლანტაციური გენეტიკური ტესტირება ანუპლოიდიის გამოსავლენად (PGT-A) NGS-მეთოდით. ორსულობის გამოსავალი ფასდებოდა ბიოქიმიური ორსულობის, თვითნებითი აბორტების და ცოცხლად შობადობის მაჩვენებლის მიხედვით. შედეგები

გაზომილი 555 ფოლიკულიდან მიღებული იქნა 508 კვერცხუჯრედი (91,5 %). მათგან მომწიფებული კვერცხუჯრედების (MII) რაოდენობა აღმოჩნდა 411 (80,9%), მოუმწიფებელი იყო 97კვერცხუჯრედი (19.2%), მოუმწიფებელი 97 კვერცხუჯრედიდან 51 იყო გერმინაციული ვეზიკულა (GV - 10.04%), 46 (9.06%) კვერცხუჯრედს არ ქონდათ პოლარული სხული (M I). ფოლეკულები ზომების მიხედვით დაიყო 4 საკვლევ ჯგუფად: ჯგუფი I - <15 მმ; ჯგუფი II - 15-18 მმ; ჯგუფი III - 18-20 მმ; ჯგუფი IV - >20 მმ. მომწიფებული კვერცხუჯრედების რაოდენობა სარწმუნოდ მაღალი იყო მეორე, მესამე და მეოთხე ჯგუფებში პირველ ჯგუფთან შედარებით, რაც მიუთითებს იმაზე, რომ ფოლიკულის ზომას აქვს მნიშვნელოვანი ეფექტი MII კვერცხუჯრედების მიღებაში ($p<0.0001$). განსაკუთრებით მეტი მომწიფებული კვერცხუჯრედები დაფიქსირდა მეორე და მესამე ჯგუფებში.

დადგინდა, რომ დიდი ზომის ფოლიკულებიდან მიღებული კვერცხუჯრედების განაყოფიერების და ბლასტოცისტის ფორმირების სიხშირე სარწმუნოდ მაღალია მცირე ზომის ფოლიკულებიდან მიღებულ კვერცხუჯრედებთან შედარებით ($p<0.0001$);

დადგინდა, რომ ეუპლოიდური ბლასტოცისტების მიღების სიხშირრე სარწმუნოდა არ განსხვავდებოდა საკვლევი ჯგუფების მიხედვით. არ დაფიქსირდა მნიშვნელოვანი ურთიერთკავშირი ფოლიკულის ზომასა და ეუპლოიდური ბლასტოცისტის ფორმირებას შორის.

იმ ქალებში, ვისთანაც ჩატარდა ერმბიონის გენეტიკური ტესტირება და გადატანილ იქნა ეუპლოიდური ემრბიონები, სარწმუნოდ დაბალი აღნოჩნდა ბიოქიმიური ორსულობის, თვითნებითი აბორტების მაჩვენებელი და სარწმუნოდ მაღალი ცოცხლად შობადობის მაჩვენებელი, მათთან შედარებით, ვისაც არ ჩაურდათ ემბრიონის განეტიკური ტესტირება .

დასკვნა

კვერცხუჯრედის მომწიფებულობა, განაყოფიერების და ბლასტოცისტის ფორმირება დამოკიდებულია ფოლიკულის ზომაზე. ფოლიკულის ზომა არ არის ბლასტოცისტის ეუპლოიდიის ინდიკატორი. პრეიმპლანტაციური გენეტიკური ტესტირება ეუპლოიდიის გამოსავლენად (PGT-A) მნიშვნელოვნად ზრდის ორსულობის მიღების და ცოცხლად შობადობის მაჩვენებელს და ამცირებს თვითნებითი აბორტების სიხშირეს.

საკვანძო სიტყვები: ფოლიკულის ზომა, კვერცხუჯრედის ხარისხი, ბლასტოცისტის პლოიდია, უჯრედის მომწიფება, ბლასტოცისტის ფორმირება, ინ ვიტრო განაყოფიერება (IVF), პრეიმპლანტაციური გენეტიკური ტესტირება ანეუპლოიიდის გამოსავლენად (PGT-A), საკვერცხეების სტიმულაცია, ეუპლოიდური ბლასტოცისტები, ორსულობის შედეგები, GnRH-ანტაგონისტის პროტოკოლი, კვერცხუჯრედის დონორი, ცოცხლად შობადობის მაჩვენებლები, თვითნებითი აბორტი.