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Expert Opinion

The Italian guidelines on non-invasive and invasive prenatal diagnosis: Executive summary of recommendations for practice the Italian Society for Obstetrics and Gynecology (SIGO)

T. Stampalija [a,b,1], T. Ghi [c,1,2,*], M. Barbieri [d], M. Morlando [e], E. Di Pasquo [f], C. Formigoni [g], E. Ferrazzi [d,h], Chair and Methodological Group, Promoting Committee, Working Group on Non-invasive Prenatal Diagnosis, Working Group on Invasive Prenatal Diagnosis, Working Group Secretariat, Panel of Experts Delegated by Scientific Societies and Stakeholders, External Auditors

[a] *Full Professor, Director of the Obstetrics and Gynecology Clinic, Department of Obstetrics, Maggiore Polyclinic Hospital, IRCCS Ca' Granda Foundation, Padiglione Mangiagalli, University of Milan, Milan, Italy*
[b] *Full Professor, Department of Clinical and Community Sciences, Maggiore Polyclinic Hospital, IRCCS Ca' Granda Foundation, Padiglione Mangiagalli, University of Milan, Milan, Italy*
[c] *Chiara Formigoni – Documentalist and Biomedical Librarian, GIDIF-RBM Steering Committee, Como, Italy*
[d] *Department of Women's and Children's Health, Women's Health Area, Fondazione IRCCS Policlinico Universitario Agostino Gemelli, Rome, Italy*
[e] *Medical Genetics Laboratory, Translational Cytogenomics Research Unit, Bambino Gesù Pediatric Hospital, Rome, Italy*
[f] *Researcher in Gynecology and Obstetrics, University of Campania "Luigi Vanvitelli", Naples, Italy*
[g] *Responsible for SSD of Obstetric and Gynecologic Ultrasonography and Prenatal Diagnosis, City of Health and Science, Turin, Italy*
[h] *Director of Fetal Medicine and Prenatal Diagnosis UOC, Di Venere Hospital, ASL BA, Bari, Italy*

Introduction

The Italian Ministry of Health, through National Committee for the Clinical Excellence, requested to national scientific societies to develop clinical guidelines on relevant topics. The GRADE (Grading of Recommendations, Assessment, Development and Evaluation) methodology was recommended [1–3]. The Italian Society for Obstetrics and Gynecology (SIGO), in collaboration with other Italian scientific societies (AGUI, AOGOI, ONDA, SIEOG, SIFES, SIMP), developed guidelines on the non-invasive and invasive prenatal testing in pregnancy [4].

Objectives

The objective of the Guideline is to provide guidance on the appropriate clinical use of non-invasive and invasive prenatal testing according to different clinical conditions. The document is intended to represent the reference standard for the healthcare professionals of the field including gynecologists, obstetricians, midwives, general practitioners, forensic scientists, as well as for the general population, in particular pregnant women or women willing to become pregnant and their partners.

Methods

Methodology

The guideline was promoted by the Italian Society of Obstetrics and Gynecology (SIGO), it was approved by the Italian Superior Health Council, and it was developed according to the standards and methodology defined by the Guidelines National System and described by the National Committee for the Clinical Excellence in 2019 [1]. GRADE methodology was used for the development of the guideline [2,3]. The Appraisal of Guidelines for Research and Evaluation Instrument (AGREE II) was used for guideline reporting [5].

The Promoting Society nominated a Promoting Committee and a Methodological Group that included a methodologist with expertise in

* Corresponding author.
E-mail address: tullio.ghi@unipr.it (T. Ghi).
[1] Equally contributing authors.
[2] On behalf of the Italian Society for Obstetrics and Gynecology (SIGO) and the Working Group.

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GRADE methodology and a librarian with expertise in systematic research of the bibliographic resources.

The Promoting Committee nominated a multidisciplinary Panel and two Working Groups, one for the topic "non-invasive testing" and the other for the topic "invasive testing". The multidisciplinary Panel included experts in the field, geneticist and stakeholders. Moreover, all Scientific Societies potentially involved in the field were contacted and those that agreed to participate nominated a representative that constituted the Panel.

Each Working Group had a coordinator and 6 to 7 members, including geneticists.

Formulation of the clinical questions

For each of the two topics of the guideline, clinical questions with main outcomes of interest were formulated and discussed by the Working Group. The clinical questions were formulated according to the Population, Intervention, Comparison, Outcome (PICO) framework. All proposed PICOs were voted by the panel and only those who were scored as relevant were used to produce a recommendation and included in the guideline.

The proposed outcomes identified for each PICO were anonymously voted by the Panel (voting score ranged from 1 (not important) to 9 (extremely important)). A maximum number of 7 outcomes was set for each PICO. Outcomes with the score 1–3 (outcome with limited importance to take a clinical decision) were discharged.

Systematic review of the literature

A systematic search of the literature was conducted according to the PICOs. It was a-priori planned to consider only guidelines of high or moderate quality. In case the search retrieved no results, systematic reviews and *meta*-analysis would have been systematically searched and, if also such search had been unsuccessful, high quality primary studies would have been considered to produce the recommendations. The systematic literature search was developed by an experienced professional librarian in March 2022, including all the available evidence since 2015. As the time needed to develop the recommendations took longer than expected due to SARS-CoV-2 pandemic, an additional systematic literature search was performed in April 2023. The details of the systematic research strategy are represented in Appendix 1.

Research and selection of guidelines

The systematic literature search was performed on Medline/PubMed, Embase, on Guideline databases and on relevant web sites pertinent to the topic. Medline/PubMed and Embase were searched utilizing combinations of the relevant medical subject heading (MeSH) terms and also by free text using the field "Text Word", in order to improve the effectiveness of the search (Appendix 1). In the web sites the research was conducted by free text using. Inclusion criteria were English/Italian language and publication date from 2015. An a priori list of criteria was decided to make the first selection of the guidelines. These criteria were: development by multidisciplinary panel, primary evidence identified through a systematic literature review, explicit grading of recommendations. Any additional relevant document suggested by the Working Group was added to the evidence in support of this guideline. The PRISMA flowcharts are reported in the Appendix 2. The methodological quality of the selected guidelines was assessed independently by two researchers from each Working Group in accordance with the AGREE II tool [5]. The summary table for each recommendation adopted/adapted from the available guidelines is provided in the Appendix 3, together with the strength and the level of evidence.

From systematic review to recommendations

The planned process to develop the guideline was significantly slowed down by the SARS-CoV-2 pandemic, which deeply impacted on the activities of the majority of the clinicians involved in the process. The two Working Groups formulated a draft document with a list of suggested recommendations for each PICOs, the supporting literature and a summary of the evidence relative to the efficacy and the safety of the proposed interventions. The document was then submitted to the Panel for the discussion and voting. Discussion was particularly focused on topics for which "complete agreement" was expressed by less than the 85 % of the Panel members. Each meeting was held on a virtual platform and recorded or documented.

The development of the recommendations was carried out by considering the balance between the desirable and undesirable effects of different intervention alternatives, in accordance with the GRADE methodology [6]. In case of inconsistencies in the assessment of this balance, the Panel expressed a "conditional" recommendation in favor or against the intervention. If the balance was clearly in favor of or against an intervention, the recommendation was considered to be "strong". However, the recommendations even when "strong" were mentioned to be intended as an informative support in the decision-making process that should take place between a woman/couple and the professional.

External revision

The final draft of the guideline was evaluated by two independent external revisors with the request to provide their comments and proposals.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have influence their work for the development of the guideline. All members signed a policy for declaring and managing potential conflict of interest.

Reccomendations

Recommendation 1

Non-invasive prenatal testing

It is recommended to offer to all women with a singleton pregnancy the combined test as a screening test for the most common chromosomal anomalies (trisomy 21, 18, and 13).

STRONG POSITIVE recommendation.

Adapted from five high-quality guidelines and one of moderate quality.

Recommendation 2

It is recommended to offer the combined test to all women, regardless of maternal age.

STRONG POSITIVE recommendation.

Adapted from five high quality guidelines and one of moderate quality.

Recommendation 3

In women with singleton pregnancy, for cost-effectiveness and feasibility reasons, it is suggested that cell-free DNA/Non-Invasive Prenatal Testing (cfDNA/NIPT) does not replace the combined test as a primary screening for the most common chromosomal anomalies.

CONDITIONAL NEGATIVE recommendation.

Adapted from two high-quality guidelines.

Recommendation 4

In women identified to be at high risk after the combined test, it is suggested to propose cfDNA/NIPT as a contingent screening, particularly for those women that do not wish to undergo invasive prenatal diagnosis testing, and following an accurate counseling (to discuss the response timing, diagnosis of other genetic anomalies through invasive prenatal testing)*.

CONDITIONAL POSITIVE recommendation.

Adapted from three high-quality Guidelines and as recommended by the Italian Superior Health Council.

*For risks ≥1:10 after the combined test, nuchal translucency ≥3.5 mm, or in the presence of major congenital anomalies, invasive prenatal testing is recommended as first line approach, due to the high prevalence of chromosomal and genetic anomalies in this group.

Recommendation 5

In pregnant women with an intermediate risk (≥1:1000) of aneuploidies at the combined test, it is suggested to use cfDNA/NIPT as a contingent test. The choice of using cfDNA/NIPT as a contingent test in the range of 1:11–1:1000 versus 1:101–1:1000 depends on the available resources, healthcare policy choices, and the women's preferences.

CONDITIONAL POSITIVE recommendation.

Adapted from a high-quality Guideline and as expressed by the Italian Superior Health Council.

Recommendation 6

In women who are found to be at low risk for aneuploidies at cfDNA/NIPT it is recommended to perform a first-trimester ultrasound with v measurement.

STRONG POSITIVE recommendation.

Adapted from two high-quality Guidelines.

Invasive prenatal testing

Recommendation 1

In women undergoing invasive prenatal diagnosis due to increased risk of fetal aneuploidies, it is recommended to perform rapid testing (QF-PCR, FISH) or chromosomal microarray analysis (CMA) in association with standard karyotype. Clinical decisions based on positive rapid tests results, concerning potential pregnancy termination, should be taken only in one of the following cases: pathological conventional chromosomal analysis on metaphase; abnormal CMA profile; and/or fetal structural anomalies.

STRONG POSITIVE recommendation.

Recommendation adapted from a high-quality guideline and a moderate-quality guideline.

Recommendation 2

It is recommended to offer genetic counseling prior to any invasive procedures to all women with a nuchal translucency > 3.5 mm at the first-trimester ultrasound or in the presence of a major fetal structural anomaly detected at 1st or 2nd trimester ultrasound (regardless of the risk resulting from the screening tests).

STRONG POSITIVE recommendation.

Recommendation adapted from high-quality guideline and one of moderate quality.

Recommendation 3

Periconceptional genetic counseling is recommended for all women with an increased a priori risk for a fetal genetic condition, following personal or family history and/or other genetic tests, in order to inform and advise the couple about disorders for which a prenatal diagnosis is feasible and about the specific test which can be performed (pre-test counseling), and in order to interpret the test results once available (post-test counseling).

STRONG POSITIVE recommendation.

Recommendation adapted from high-quality guideline and one of moderate quality.

Recommendation 4

In women with known Hepatitis B Virus, Hepatitis C Virus, or Human Immunodeficiency Virus infection who are eligible to an invasive prenatal testing, it is recommended to carefully assess the risk/benefit considering the potential transmission of the pathogen to the fetus. Whether an invasive prenatal diagnosis is to be performed, amniocentesis is to be preferred over chorionic villus sampling, avoiding needle insertion through the placenta whenever possible.

STRONG POSITIVE recommendation.

Recommendation adapted from a high-quality guideline and one of moderate quality.

Recommendation 5

Based on limited existing evidence, discontinuation of antiplatelet and/or anticoagulant prophylaxis prior to invasive prenatal diagnostic procedures is not suggested.

CONDITIONAL NEGATIVE recommendation

Recommendation adapted from a moderate-quality guideline.

Recommendation 6

Invasive prenatal diagnostic procedures are recommended to be performed in centers where appropriate equipment and facilities, adequate training of operators, adequate auditing of procedures, and the possibility of interdisciplinary consultations can be guaranteed.

STRONG POSITIVE recommendation

Recommendation adapted from a high-quality guideline and a moderate-quality guideline.

CRediT authorship contribution statement

T. Stampalija: Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft. **T. Ghi:** Conceptualization, Data curation, Formal analysis, Investigation, Supervision, Writing – original draft, Writing – review & editing. **M. Barbieri:** Data curation, Writing – review & editing. **M. Morlando:** Validation, Writing – original draft, Writing – review & editing, Conceptualization. **E. Di Pasquo:** Conceptualization, Validation, Writing – original draft, Writing – review & editing. **C. Formigoni:** Data curation, Formal analysis, Methodology, Validation. **E. Ferrazzi:** Conceptualization, Methodology, Formal analysis, Supervision, Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments and working groups

CHAIR AND METHODOLOGICAL GROUP: Enrico M. Ferrazzi – Coordinator. Full Professor, Director of the Obstetrics and Gynecology Clinic, Department of Obstetrics, Maggiore Polyclinic Hospital, IRCCS Ca' Granda Foundation, Padiglione Mangiagalli, University of Milan, Milan, Italy. Fabio Parazzini – Methodologist. Full Professor, Department of Clinical and Community Sciences, Maggiore Polyclinic Hospital, IRCCS Ca' Granda Foundation, Padiglione Mangiagalli, University of Milan, Milan, Italy. Chiara Formigoni – Documentalist and Biomedical Librarian. GIDIF-RBM Steering Committee, Como.

PROMOTING COMMITTEE: Enrico M. Ferrazzi – Coordinator. Full Professor, Director of the Obstetrics and Gynecology Clinic, Department of Obstetrics, Maggiore Polyclinic Hospital, IRCCS Ca' Granda Foundation, Padiglione Mangiagalli, University of Milan, Milan, Italy. Tamara Stampalija – Associate Professor, Director of Fetal Medicine and Prenatal Diagnosis SSD, IRCCS Burlo Garofolo, University of Trieste, Trieste. Tullio Ghi - Full Professor, Director of the Obstetrics and Gynecology Clinic, University of Parma, Parma.

WORKING GROUP on NON-INVASIVE PRENATAL DIAGNOSIS: Tamara Stampalija – Coordinator. Associate Professor, Director of Fetal Medicine and Prenatal Diagnosis SSD, IRCCS Burlo Garofolo, University of Trieste, Trieste. Daniela Anzelmo – Consultant, Family Planning Clinic Caltanisetta 2. Valentina De Robertis – Consultant, Fetal Medicine and Prenatal Diagnosis UOC, Di Venere Hospital, ASL BA, Bari. Marco De Santis – Consultant, Department of Women's and Children's Health, Women's Health Area, Fondazione IRCCS Policlinico Universitario Agostino Gemelli, Rome. Antonio Novelli – Director, Medical Genetics Laboratory, Translational Cytogenomics Research Unit, Bambino Gesù Pediatric Hospital, Rome. Maddalena Morlando - Researcher in Gynecology and Obstetrics, University of Campania "Luigi Vanvitelli", Naples. Andrea Sciarrone - Consultant, Responsible for SSD of Obstetric and Gynecologic Ultrasonography and Prenatal Diagnosis, City of Health and Science, Turin. Paolo Volpe - Consultant, Director of Fetal Medicine and Prenatal Diagnosis UOC, Di Venere Hospital, ASL BA, Bari.

WORKING GROUP on INVASIVE PRENATAL DIAGNOSIS: Tullio Ghi – Coordinator. Full Professor, Director of the Obstetrics and Gynecology Clinic, University of Parma. Giancarlo Conoscenti - Consultant, Obstetrics and Gynecology Division, Cannizzaro Emergency Hospital, Catania. Elvira Di Pasquo – Consultant, Department of Medicine and Surgery, Obstetrics and Gynecology Unit, University of Parma, Parma. Sabrina Giglio - Departments of Medical Sciences, Public Health and Medical Genetics, Binaghi Hospital, Cagliari. Claudio Giorlandino - Specialist Surgeon in Gynecology and Obstetrics, Rome. Giovanni Monni - Consultant, Director of the Complex Structure of Human Reproduction Pathophysiology and Prenatal Diagnosis P.O. Microcitemico "A. Cao", ARNAS Brotzu, Cagliari. Fabrizio Taddei - Consultant, Director of Gynecology and Obstetrics UOC, Rovereto and Trento Hospital ASST Trento, Trento.

WORKING GROUP SECRETARIAT: Moira Barbieri – Medical Specialist in Gynecology and Obstetrics Training, Maggiore Polyclinic Hospital, IRCCS Ca' Granda Foundation, University of Milan, Milan, Italy.

PANEL OF EXPERTS DELEGATED BY SCIENTIFIC SOCIETIES AND STAKEHOLDERS: Andrea Dall'Asta, AGUI - Department of Metabolism, Digestion and Reproduction, Institute of Reproductive Biology and Development, Department of Medicine and Surgery, Obstetrics and Gynecology Unit, University of Parma, Parma. Elsa Viora, AOGOI - Obstetric-Gynecological Ultrasound Unit, Department of Obstetrics and Gynecology, Sant'Anna Hospital, Turin. Tiziana Frusca, SIEOG - Department of Obstetrics and Gynecology, University of Parma, Parma. Antonio Ragusa. SIGO - Department of Obstetrics and Gynecology, Fatebenefratelli Hospital, Isola Tiberina, Rome. Maurizio Guido, SIFES - San Salvatore Hospital L'Aquila, Gynecology and Obstetrics UOC, L'Aquila. Achille Iolascon, SIGU - Department of Molecular Medicine and Medical Biotechnology, University of Naples Federico II, Naples; CEINGE Advanced Biotechnologies, Naples. Herbert Valensise, SIMP - Department of Surgical Sciences, Tor Vergata University of Rome, Rome, Italy; Department of Obstetrics and Gynecology, Casilino Policlinic, Rome. Nicoletta Orthmann, ONDA - Medical-scientific coordinator of Onda Foundation - National Observatory on Women's Health and Gender.

EXTERNAL AUDITORS: Federico Prefumo - Director of the Obstetrics and Gynecology UOC, IRCCS Giannina Gaslini Institute, Genoa. Rinaldo Zanini – Member of the National Birth Path Committee. Former Director of the Maternal and Child Management Department, Azienda Ospedaliera "Provincia di Lecco", Lecco.

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