Anticonceptivos, más allá de la anticoncepción

Dra. Zarela Lizbeth Chinolla Arellano

Antes de dar anticonceptivos, es necesario hacer el **uso de la historia clínica**, interrogar a la paciente para verificar los factores de riesgo que tenemos con cada una de ellas.

Los **criterios de elegibilidad de la OMS** nos indican cuáles son las contraindicaciones para su uso, aunque la gran mayoría de las pacientes no las tienen.

Reducir riesgos y morbilidades

El hecho de que una paciente **tenga un riesgo para el uso de un anticonceptivo, pero también tenga el beneficio**, debe de ser un reto para el médico al utilizarlo y tratar de disminuir la reducción del riesgo, es decir, buscar siempre el beneficio de la paciente.

Características de los anticonceptivos

Todos los hormonales combinados tienen **estrógenos y progesterona**. Los estrógenos pueden ser el **estradiol o etinilestradiol**, en gramaje de 20, 30 y 15 microgramos. Existían dosis más altas que ya no se encuentra en el mercado porque aumentan el riesgo cardiovascular. Todos los anticonceptivos que están entre 20 y 30 microgramos son muy seguros.

Elección del anticonceptivo

La manera de elegir un anticonceptivo solo o combinado, ya sea para una cuestión anticonceptiva u otra condición, **tiene que ver con la progestina, ya que hay progestinas que tienen efecto androgénico, antiandrogénico, antimineralocorticoide o glucocorticoides**, por lo que es el elemento principal del anticonceptivo porque va a generar el efecto anovulatorio. Por esta razón, no hay anticonceptivos solamente de estrógenos.

Los **estrógenos combinados con progestinas** es la manera más fisiología de anticoncepción o un tratamiento para otra patología, o de **progestágenos** que pueden generar más efectos secundarios en la paciente.

Clasificación de las progestinas

Las progestinas provienen del colesterol y unas son de **derivadas de la alfa hidroxi progesterona**, otras derivan de la norprogesterona o de la nortestosterona.

También se pueden clasificar por la manera en que fueron saliendo al mercado. Primera, segunda, tercera o cuarta generación. Los de primera generación no son peores o mejores que los de cuarta, todas tienen un beneficio.

Hablando de **anovulatorios**, **levonorgestrel** es la progestina más utilizada, aunque no tiene un efecto antiandrogénico, por lo que no tiene un efecto adicional como en la piel, cuando buscamos una doble partida para el tratamiento de nuestras pacientes. La **ciproterona** tiene un efecto antiandrogénico, por ejemplo en el síndrome de ovario poliquístico (SOP), o en las pacientes cuando suben de peso o las que tienen hipotiroidismo y que simulan un ovario poliquístico. La **drospiredona** tiene un efecto antimineralocorticoide, lo que evita la retención de líquidos.

Una de las preguntas frecuentes es **"¿voy a subir de peso?"**. Sí, si no se cuidan. No, si se lleva una dieta o se quitan los factores de riesgo, porque lo que genera el aumento de peso es el estilo de vida, su régimen alimenticio muy determinado.

La **drospirenona** tiene buenos efectos a nivel de andrógenos ováricos, por lo tanto, es una buena elección para ciertos casos de SOP. El **dienogest** es una de las mejores progestinas, principalmente para pacientes con dolor pélvico crónico, endometriosis, dismenorrea, síndrome disfórico premenstrual, por lo que es una muy buena alternativa para procesos inflamatorios, ya sea adenomiosis, adenomatosis o endometriosis.

La **clormadinona** es una de las progestinas más antigua y más utilizada, con poco efecto antiandrogénico. Por lo que hay que buscar los beneficios fisiológicos, preventivos o terapéuticos adicionales de los anticonceptivos.

Es importante un buen interrogatorio para determinar las características del ciclo menstrual. **La duración del sangrado tiene que ser de 3 a 7 días, con un volumen de 5 a 80 ml y una frecuencia de 24 a 35 días más menos 1**, por lo que si se sale de estos parámetros, la paciente amerita tratamiento con un anticonceptivo, ya que de manera fisiológica, todos pueden regular el ciclo menstrual. Además se puede regular el **aumento del sangrado**, que puede generar **anemia**, que es lo más frecuente a nivel mundial y más en las mujeres en etapa reproductiva, por la pérdida mes con mes.

La **dismenorrea** es otro padecimiento común que puede ser tratado. Esta puede ser primaria o secundaria. La **primaria** se presenta cuando la paciente comienza a menstruar y no hay otra patología. Por lo que si presenta dolor suficiente para cambiar su estilo de vida, tomar analgésicos o disminuir sus actividades cotidianas, es necesario el tratamiento. El interrogatorio nos dirá si sí es candidata a los anticonceptivos hormonales combinados, incluso si la paciente es **adolescente**, tiene que recibir tratamiento una vez que se inicia la menarquia, que no es sinónimo de pubertad precoz o pubertad retardada, donde se tiene que redireccionar al endocrinólogo o biólogo a la reproducción. Pero si no tiene estas condiciones y tiene el peso y talla correspondiente a la etapa cronológica, hay que darlo tratamiento.

Las pacientes que están en **etapa perimenopáusica entre los 38 a 48 años**, es normal que tengan una **disfunción anovulatoria** con o sin síntomas vasomotores o síntomas que asemejan al climaterio, se pueden beneficiar de ciertas dosis de anticonceptivos según sus factores de riesgo.

Los **anticonceptivos mejoran la densidad mineral ósea**, sobre todo en las jóvenes en que tienen disfunción parcial, no como para diagnosticar menopausia precoz o temprana, pero que sí necesiten sustitución hormonal. Las mujeres con riesgo de **osteopenia** se ven beneficiadas, sobre todo aquellas con un índice de masa corporal muy bajo o tratamientos crónicos con corticoesteroides, metotrexato o hipotiroidismo. Todo esto puede ser que beneficie a la paciente. La mejoría de la masa ósea en general es muy buena.

Los **trastornos menstruales** se hacen comunes después de los 40 años con sangrados abundantes, los que se van a abolir con el uso de los **hormonales combinados**. Es importante recordar que **no es terapia de reemplazo hormonal** porque las dosis son diferentes.

Por lo que la **anticoncepción en una mujer entre 40 y 45 años** tendrá beneficios solo si se utilizan hormonales combinados.

Los **anticonceptivos también nos ayudan a prevenir patologías**. Cuando estamos hablando de **sangrado uterino normal**, generado por pólipos, miomas, adenomiosis o alteraciones en el endometrio o cuestiones funcionales, la primera línea de tratamiento son los **anticonceptivos combinados**. En la **miomatosis uterina** son la primera línea de tratamiento, porque necesitamos regular y contrarregular los receptores monoclonales que tienen estos miomas, aunque no va a disminuir el tamaño del mioma ni la probabilidad de sangrado por miomas submucosos. **De manera inicial daremos hormonales a dosis normales o a dosis dobles durante 7 o 14 días** para saturar los receptores y muchas veces disminuye el sangrado. Por los que los hormonales combinados pueden regular los ciclos, disminuir la cantidad de endometrio, el sangrado y el 30 al 40% serán asintomáticos, según la edad y la localización del mioma. Si el **mioma es intramural o cavitario**, el tratamiento es quirúrgico, pero se pueden utilizar para mitigar los síntomas descritos.

En la **endometriosis**, los hormonales combinados no están contraindicados. Al contrario, en una endometriosis leve o moderada o posterior una cirugía de un endometrioma, se debe de dar tratamiento, ya que si no se hace, en 6 meses, un año o 18 meses va a recidivar. Es importante tener en mente que los hormonales combinados van a limitar la ovulación, ya que van a evitar que los niveles de estrógenos se eleven, lo que evita la posibilidad de que estos generan el proceso inflamatorio o la enfermedad.

Las **progestinas** son un tratamiento muy adecuado en endometriosis moderada o severa o en endometriomas, pero pueden generar bochornos y resequedad vaginal. Los **análogos de la GnRH** no se usan por más de seis meses, ya que

tienen efectos deletéreos para la densidad mineral ósea o la descalcificación y generan bochornos. En el tratamiento de la endometriosis, cuando la paciente no tolera la terapia con análogos de la GnRH, se le puede dar hormonales combinados de manera más fisiológica, sobre todo en pacientes jóvenes. Por lo que es importante considerarlos como primera línea para largo plazo, sobre todo para pacientes que han tenido largos tratamientos con análogos como danazol o progestinas y que ya no los toleran y que requieren su restitución de estrógenos.

En el **SOP**, el dato pivote principal es el aumento de los estrógenos y los andrógenos. Por lo que hay que **verificar el fenotipo**, para identificar dónde se está generando la secreción anómala de andrógenos, que pueden ser los ovarios, las suprarrenales y de manera periférica. Si el SOP es por secreción anómala de andrógenos a nivel ovárico, se debe suprimir el funcionamiento, y la mejor manera son con anticonceptivos combinados. Por lo que si el SOP es de origen periférico u ovárico, los hormonales combinados son una buena opción.

El **engrosamiento endometrial** ya sea por SOP, obesidad o por uso de suplementos, puede terminar en hiperplasia y esta, en **cáncer de endometrio**. Por lo que hay que definir los factores de riesgo, determinar si el endometrio está hipertrófico y posteriormente se hace hiperplásico, a ese se le indica tratamiento. Los hormonales combinados son una alternativa porque van a descamar el endometrio. Por ello, para hacer el diagnóstico necesitamos una biopsia. Se puede omitir la biopsia dependiendo del caso y los factores de riesgo. Por tanto, los **hormonales combinados nos ayudan a disminuir la posibilidad a largo plazo de cáncer ginecológico**.

Una de las **restricciones para el uso de anticonceptivos hormonales** es el riesgo de **cáncer de mama**, pero en las mujeres que no tiene este factor de riesgo, no se incrementa su riesgo de padecer este tipo de cáncer. Con respecto a las **progestinas**, los estudios no son concluyentes, por lo que solo se contraindicarán cuando haya riesgo de cáncer de mama por factores genéticos.

En el **cáncer de endometrio** tiene que ver con factores de riesgo principalmente asociados al síndrome metabólico, diabetes, hipertensión, cáncer, dislipidemia. Por lo que al corregir los factores de riesgo, podemos utilizarlos para regular el ciclo y generar la descamación del endometrio.

Con respecto al **cáncer de ovario**, se sabe que el uso de anticonceptivos durante 5 años seguidos, disminuye su riesgo, lo mismo para el **cáncer colorrectal**, sobre todo cuando se combina con el cáncer de ovario. En el **cáncer de cérvix** que tiene como factor de riesgo principal al VPH, por lo que si la paciente tiene VPH de alto riesgo y sea fumadora, hace que no sea candidata para anticonceptivos hormonales combinados.

Varios estudios, especialmente metanálisis, para cáncer de ovario, cáncer de endometrio y ciertos tipos de cáncer colorrectal, sobre todo el asociado con el

síndrome de Lynch, han demostrado que los anticonceptivos tienen un papel importante en la prevención.

Conclusiones

Las hormonas se deben usar siempre a favor de las pacientes, independientemente del proceso anticonceptivo. Es importante hacer hincapié los beneficios adicionales. Recordarle a la paciente que una vez que se suspende su uso, no es necesaria la "desintoxicación". Entre 24 a 72 horas, la depuración va a ser casi completa.

Si no se restituye inmediatamente la menstruación, hay que buscar una **disfunción ovárica**, ver la edad de la paciente, revisar el endometrio y otros factores que puedan estar alterando su ciclo.

En el caso de que la paciente no sea constante con su toma hormonal, hacer una prueba de embarazo, y recordarle que el anticonceptivo combinado no genera ningún riesgo en el embarazo.

Recordando que las **progesteronas** son las que dan la pauta para verificar cuál es el que le beneficia o le favorece más a nuestro paciente.

OPEN ACCESS

More than just contraception: the impact of the levonorgestrel-releasing intrauterine system on public health over 30 years

Kristina Gemzell-Danielsson,[1] Ali Kubba,[2] Cecilia Caetano,[3] Thomas Faustmann,[4] Eeva Lukkari-Lax,[5] Oskari Heikinheimo [6]

[1]Department of Women's & Children's Health, Karolinska Institutet, and Karolinska University Hospital, Stockholm, Sweden
[2]Department of Gynecology, Guys and St Thomas NHS Foundation Trust, London, UK
[3]Medical Affairs, Bayer Consumer Care AG, Basel, Switzerland
[4]Medical Affairs, Bayer AG, Berlin, Germany
[5]Clinical Development, Bayer Oy, Espoo, Finland
[6]Department of Obstetrics and Gynecology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

Correspondence to
Dr Cecilia Caetano, Medical Affairs, Bayer Consumer Care AG, 4002 Basel, Switzerland; cecilia.caetano@bayer.com

Received 18 November 2020
Revised 12 January 2021
Accepted 13 January 2021
Published Online First 29 January 2021

Check for updates

© Author(s) (or their employer(s)) 2021. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Gemzell-Danielsson K, Kubba A, Caetano C, *et al*. *BMJ Sex Reprod Health* 2021;**47**:228–230.

ABSTRACT

Universal access to sexual and reproductive health services is essential to facilitate the empowerment of women and achievement of gender equality. Increasing access to modern methods of contraception can reduce the incidence of unplanned pregnancy and decrease maternal mortality. Long-acting reversible contraceptives (LARCs) offer high contraceptive efficacy as well as cost-efficacy, providing benefits for both women and healthcare systems. The levonorgestrel-releasing intrauterine system (LNG-IUS) first became available in 1990 with the introduction of Mirena (LNG-IUS 20), a highly effective contraceptive which can reduce menstrual blood loss and provide other therapeutic benefits. The impact of the LNG-IUS on society has been wide ranging, including decreasing the need for abortion, reducing the number of surgical sterilisation procedures performed, as well as reducing the number of hysterectomies carried out for issues such as heavy menstrual bleeding (HMB). In the context of the COVID-19 pandemic, Mirena can provide a treatment option for women with gynaecological issues such as HMB without organic pathology, minimising exposure to the hospital environment and reducing waiting times for surgical appointments. Looking to the future, research and development in the field of the LNG-IUS continues to expand our understanding of these contraceptives in clinical practice and offers the potential to further expand the choices available to women, allowing them to select the option that best meets their needs.

BACKGROUND

Sexual and reproductive health (SRH) constitutes a fundamental human right and plays a vital role in the empowerment of women and helping achieve gender equality. Universal access to SRH services is essential to achieving this objective.[1 2] Increasing access to modern, effective methods of contraception can reduce the incidence of unplanned pregnancy, decrease maternal mortality, and can also contribute to fighting poverty.[1 3 4]

Long-acting reversible contraceptives (LARCs), such as implants, and hormonal and non-hormonal intrauterine devices (IUDs), are not only highly effective at preventing unintended pregnancy and subsequent abortion but are also cost-effective options that provide benefits for both women and healthcare systems.

Mirena (Bayer AG, Berlin, Germany) was the first levonorgestrel-releasing intrauterine system (LNG-IUS) of its kind. Developed by the Population Council's International Committee for Contraception Research, Mirena (also termed LNG-IUS 20 based on the average in vivo LNG release rate over the first year[5]) became available in 1990 in Finland under the name Levonova. Mirena is a highly effective contraceptive, with a long-lasting but reversible effect that does not require a daily routine. It also reduces menstrual blood loss, which women often find beneficial. Additionally, Mirena has therapeutic benefits; it is an effective treatment for heavy menstrual bleeding (HMB) without an organic cause and dysmenorrhoea, as well as providing endometrial protection for peri- and postmenopausal women receiving menopausal hormone therapy.

The impact of the LNG-IUS on society has been wide ranging: from decreasing the need for abortion (ie, unwanted pregnancy),[6 7] to reducing the number of surgical sterilisation procedures

performed,[8] as well as reducing the number of hysterectomies carried out for issues such as HMB without an organic cause,[9 10] allowing women to avoid an invasive surgical procedure and maintain their fertility.

NOW MORE THAN EVER: THE ROLE OF LARCS IN THE CHANGING HEALTHCARE LANDSCAPE

With the COVID-19 pandemic causing widespread disruption to the provision of healthcare, including contraceptive services and supply chains, there are bound to be concerns regarding the potential for increased unintended pregnancies.[11]

Unlike short-acting methods such as oral contraceptive pills, long-acting methods provide effective contraception for years after a single intervention that can mitigate concerns regarding access to and availability of contraceptive services.

As we seek to preserve capacity in healthcare systems and save valuable resources while increasing access to all, a shift towards medical treatment delivered in community settings for issues such as HMB is taking place in clinical practice. Medical options are less invasive than surgical treatments, generally preserve fertility, and in most cases can be prescribed and implemented rapidly and easily. In the context of the COVID-19 pandemic, the therapeutic benefits of Mirena provide an option for treating women with conditions such as HMB without an organic cause or dysmenorrhoea that minimises exposure to the hospital environment and reduces lengthy waits for surgical appointments.

BEYOND GYNAECOLOGICAL PRACTICE: HOW EFFECTIVE CONTRACEPTION CAN EMPOWER WOMEN

Increasing awareness and access to contraception can help women in low-income settings, by mitigating poverty and challenging gender inequalities. By providing discrete, effective contraception and reducing menstrual bleeding in the majority of users, the LNG-IUS can facilitate women's increased productivity and participation in society, as well as reducing some of the issues caused by limited access to sanitary protection (menstrual poverty) and providing freedom from social stigma and exclusion.

Effective contraception for women living with comorbidities, such as HIV/AIDS or anaemia, is also vital to ensure a well-timed pregnancy that occurs when they are in optimal health and is not associated with further negative health consequences. Not only does Mirena contribute to preventing unplanned pregnancy in these women, but the associated decrease in menstrual blood loss can have the additional benefit of reducing exposure to infected blood in the context of HIV/AIDS,[12 13] and improving the body's iron stores in the context of anaemia.

The reduced number of visits to healthcare providers (eg, to obtain repeat prescriptions) and reduced need to purchase sanitary protection also decreases the economic burden both to women and the healthcare system.

By decreasing the amount of sanitary protection, packaging and other waste products, the LNG-IUS and other long-acting methods can also be seen as 'green contraceptives' that reduce the traffic of non-biodegradable items to landfill sites.

THE FUTURE OF THE LNG-IUS AND PUBLIC HEALTH

With the popularity of LARCs, especially the LNG-IUS, continuing to increase it is good to know that research in this field is keeping pace. Real-world studies continue to deepen our understanding of how the LNG-IUS performs in clinical practice and further controlled trials offer the potential to expand or extend its use. Additionally, next-generation IUDs are being explored, which could further expand the options available to women, allowing them to choose the method that is best suited to their needs.[14] Moving forward, it seems reasonable to hope that with further developments and ongoing initiatives, access to LARCs will become a possibility for women across the globe.

Contributors Kristina Gemzell-Danielsson, Ali Kubba, Oskari Heikinheimo and Cecilia Caetano developed the concept for the manuscript. Thomas Faustmann and Eeva Lukkari-Lax critically reviewed and refined the concept. All authors reviewed each subsequent draft and provided detailed feedback. All authors reviewed and approved the final draft for submission.

Funding The authors would like to acknowledge Highfield, Oxford, UK for providing medical writing assistance with funding from Bayer AG.

Competing interests Kristina Gemzell-Danielsson has been an ad hoc advisory board member or invited to give presentations for Merck (MSD), Bayer, Exelgyn, Actavis, Gedeon Richter, Mithra, Exeltis, Ferring, Natural Cycles, Azanta, Gynuity, Campus Pharma and HRA-Pharma. Oskari Heikinheimo serves occasionally on advisory boards for Bayer AG, Gedeon Richter, Sandoz and Vifor Pharma, and has lectured at educational events organised by these companies. Ali Kubba has taken part in sponsored educational activity and served on advisory boards for pharmaceutical companies including Bayer, Merck and Exeltis. Thomas Faustmann is an employee of Bayer AG, Berlin, Germany. Cecilia Caetano is an employee of Bayer Consumer Care AG, Basel, Switzerland. Eeva Lukkari-Lax is an employee of Bayer Oy, Espoo, Finland.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-

commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iD
Oskari Heikinheimo http://orcid.org/0000-0002-8671-130X

REFERENCES

1 European Parliamentary Assembly. Resolution 2331. Empowering women: promoting access to contraception in Europe, 2020. Available: http://www.europeanrights.eu/public/atti/Resolution_2331_(2020)_ENG.pdf [Accessed 11 Sep 2020].
2 United Nations. Sustainable Development Goals. Available: https://www.un.org/sustainabledevelopment/sustainable-development-goals/ [Accessed 11 Sep 2020].
3 Brunson J. Tool of economic development, metric of global health: promoting planned families and economized life in Nepal. *Soc Sci Med* 2020;254:112298.
4 Sawhill IV, Guyot K. Preventing unplanned pregnancy: lessons from the States Brookings Institution, 2019. Available: https://www.brookings.edu/wp-content/uploads/2019/06/Preventing-Unplanned-Pregnancy-2.pdf [Accessed 11 Sep 2020].
5 Hofmann BM, Apter D, Bitzer J, *et al*. Comparative pharmacokinetic analysis of levonorgestrel-releasing intrauterine systems and levonorgestrel-containing contraceptives with oral or subdermal administration route. *Eur J Contracept Reprod Health Care* 2020;25:417–26.
6 Peipert JF, Madden T, Allsworth JE, *et al*. Preventing unintended pregnancies by providing no-cost contraception. *Obstet Gynecol* 2012;120:1291–7.
7 Pohjoranta E, Suhonen S, Gissler M, *et al*. Early provision of intrauterine contraception as part of abortion care–5-year results of a randomised controlled trial. *Hum Reprod* 2020;35:796–804.
8 Grimes DA, Mishell DR. Intrauterine contraception as an alternative to interval tubal sterilization. *Contraception* 2008;77:6–9.
9 Dhamangaonkar PC, Anuradha K, Saxena A. Levonorgestrel intrauterine system (Mirena): an emerging tool for conservative treatment of abnormal uterine bleeding. *J Midlife Health* 2015;6:26–30.
10 Meaidi A, Kuhr Skals R, Alexander Gerds T, *et al*. Decline in Danish use of oral tranexamic acid with increasing use of the levonorgestrel-releasing intrauterine system: a nationwide drug utilization study. *Contraception* 2020;101:321–6.
11 Ferreira-Filho ES, de Melo NR, Sorpreso ICE. Contraception and reproductive planning during the COVID-19 pandemic. *Expert Rev Clin Pharmacol* 2020;13:615–22.
12 Heikinheimo O, Lehtovirta P, Suni J, *et al*. The levonorgestrel-releasing intrauterine system (LNG-IUS) in HIV-infected women–effects on bleeding patterns, ovarian function and genital shedding of HIV. *Hum Reprod* 2006;21:2857–61.
13 Kakaire O, Tumwesigye NM, Byamugisha JK, *et al*. Acceptability of intrauterine contraception among women living with human immunodeficiency virus: a randomised clinical trial. *Eur J Contracept Reprod Health Care* 2016;21:220–6.
14 Grandi G, Farulla A, Sileo FG, *et al*. Levonorgestrel-releasing intra-uterine systems as female contraceptives. *Expert Opin Pharmacother* 2018;19:677–86.

International Journal of Women's Health

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Contraception During Perimenopause: Practical Guidance

Giovanni Grandi[1], Pierluigi Di Vinci[2], Alice Sgandurra[1], Lia Feliciello[1], Francesca Monari[1], Fabio Facchinetti[1]

[1]Department of Medical and Surgical Sciences for Mother, Child and Adult, University of Modena and Reggio Emilia, Azienda Ospedaliero Universitaria Policlinico, Modena, 41124, Italy; [2]International Doctorate School in Clinical and Experimental Medicine, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, 41124, Italy

Correspondence: Giovanni Grandi, Department of Medical and Surgical Sciences for Mother, Child and Adult, University of Modena and Reggio Emilia, Azienda Ospedaliero Universitaria Policlinico, Via del Pozzo 71, Modena, 41124, Italy, Tel +39 059 422 2665, Email giovanni.grandi@unimore.it

Abstract: Climacteric is by no means in itself a contraindication to safe contraception. On the contrary, there are several conditions related to the perimenopause that could benefit from the use of modern contraceptives, mainly hormonal, with the goals of avoiding unintended pregnancies and giving further possible benefits beyond contraception (menstrual cycle control, a reduction of vasomotor symptoms and menstrual migraines, a protection against bone loss, a positive oncological risk/benefit balance). This narrative review aims to provide practical guidance on their possible use in this particular life stage, both short- and long-acting reversible contraceptives, and to assist clinicians for women transitioning from contraception to their menopausal years, including the possible initiation of postmenopausal hormone therapy. Comprehensive contraceptive counselling is an essential aspect of the overall health and wellbeing of women and should be addressed with each such patient irrespective of age.

Keywords: contraception, perimenopause, SARCs, LARCs, oral contraceptives, combined oral contraceptives, vaginal rings, patch, intrauterine devices, implants, forties, metabolism

Contraception in Perimenopause: Is There Need or Not?

The perimenopause is the period that precedes the menopause and is roughly a synonym of "menopausal transition". It corresponds to the stages −1 and −2 according to the STRAW+10 Staging System for Reproductive Aging in Women,[1] beginning when there is a variable persistent length of ≥7-day difference of consecutive menstrual cycles plus supportive clinical and endocrinological criteria.[1]

It starts 5–10 years before the menopause, at approximately 40 years of age.[2] Since the population is aging, the total number of women aged 40–49 years is increasing by 32% in Europe. As defined by the Stages of Reproductive Aging Workshop (STRAW) criteria, the term perimenopause or menopausal transition covers the transition from reproductive age through to menopause, ie, early perimenopause (stage −2), late perimenopause (stage −1), the last menstrual period (stage 0) and early post-menopause (stage +1).[3] The principal criteria for entry into the early perimenopause include the onset of irregular or "variable length" cycles with at least 7-day differences in cycle length between consecutive cycles or a cycle length <25 days or >35 days. Late perimenopause starts once the cycles exceed 60 days in length.

This period is characterised by several changes in the hormonal milieu of a woman: a reduction in the number of primordial follicles is demonstrated due to the lower levels of inhibin B and Anti-Müllerian Hormone (AMH)[4] and the ovaries begin to decrease in weight and size.[5] This is associated with an increase in follicle stimulating hormone (FSH) levels due to the decrease in oestradiol (E2) and inhibin B in the serum, which are fundamental to its negative feedback, while progesterone levels control luteinising hormone (LH).[5] Moreover, the low levels of E2 cannot induce the LH peak that is necessary for ovulation. Therefore, due to these hormonal changes, the occurrence of anovulatory cycles increases and the interval between two ovarian cycles tends to be variable in length.[6] The result is that the fertility of a woman during the perimenopause is lower but, at the same time, there are higher rates of unintended pregnancies among these

Received: 6 February 2022
Accepted: 7 July 2022
Published: 15 July 2022

© 2022 Grandi et al. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms.php and incorporate the Creative Commons Attribution – Non Commercial (unported, v3.0) License (http://creativecommons.org/licenses/by-nc/3.0/). By accessing the work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, please see paragraphs 4.2 and 5 of our Terms (https://www.dovepress.com/terms.php).

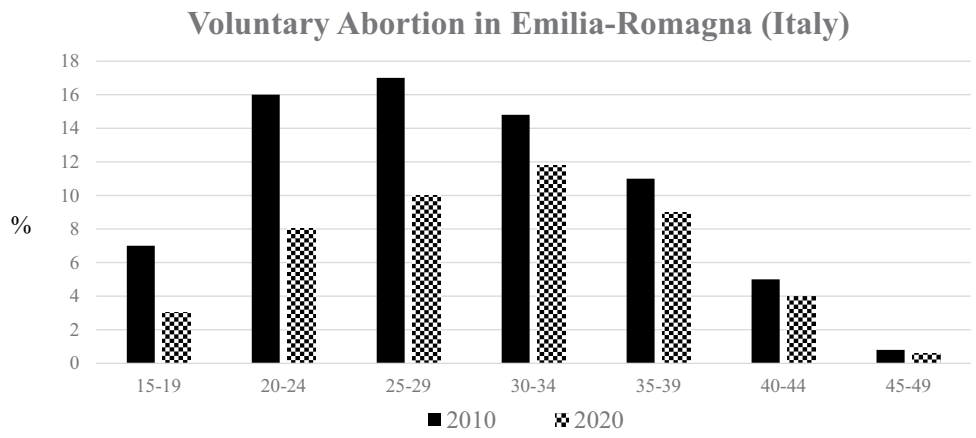

Figure 1 Comparisons between the percentage of voluntary abortions between 2010 and 2020 according to the different age groups in the Emilia-Romagna region (Italy).
Notes: Data from: Regione Emilia-Romagna. Salute. Assessorato politiche per la salute; Relazione sull'interruzione volontaria digravidanza in Emilia-Romagna nel 2020 [Health Policy Department; Report on the voluntary termination of pregnancy in Emilia-Romagna in 2020]; 2021. Available from: https://salute.regione.emilia-romagna.it/siseps/applicazioni/ig/documentazione. Accessed February 1, 2022. Italian.[101]

women.[7] Women over 40 have lower fecundity (chance of a live birth per menstrual cycle) compared with their younger cohort. The annual risk of pregnancy is clearly lower than that in younger women: 10% at 40–44 years to only 2–3% at 45–49 years.[8] Although the risk of pregnancy is lower in this age group, the acceptance of pregnancy is also reduced with more women having elective abortions, so there is an important need for contraception. In 2006, the overall rate of unintended pregnancy in the United States was 49%, of which 48% represents women aged 40–44.[9]

In Italy, the abortions in this lifestage (>40 years old) were 8140 out of 65,757 total abortions in 2020 (12%) (http://dati.istat.it/Index.aspx?DataSetCode=DCIS_IVG_CARATTDON). This is the only phase of life in which abortions are not significantly decreasing from 2010 to 2020 in our Italian region, Emilia-Romagna (Figure 1) (https://salute.regione.emilia-romagna.it/siseps/applicazioni/ig/documentazione). In addition, these "late" pregnancies can be complicated by several factors, such as higher risk of miscarriages, chromosomal abnormalities (due to the poorer quality of oocytes generated in metaphase over 40 years[10]), ectopic pregnancy, preeclampsia and post-partum haemorrhage risk.[11] In 2011, women aged 40–44 experienced spontaneous abortion at a rate of 34%, while women aged 45 and older reported a rate of 53% for ongoing pregnancies. Moreover, the age-related issues associated with the use of hormonal therapies must be analysed.[12] Importantly, among them is the increased risk of cancer, the possible occurrence of osteopenia and osteoporosis, the risk of thromboembolism, psychological changes and the possible sexual dysfunction associated with this peculiar late reproductive period.[13] Regarding the thromboembolic risk, it is strictly related to hypertension and cardiovascular diseases in general, as well as obesity and metabolic syndrome, whose incidence rises with age.[14]

Finally, another important problem often experienced during the climacteric period is represented by the abnormalities related to abnormal uterine bleeding (AUB), due to both organic and dysfunctional factors,[15] which have a strong impact on the woman's life.[16] Therefore, in the fourth and fifth decades of life in women there is a noticeable incidence of adenomyosis, polyps and fibroids, which are possible organic causes of AUB.[17] Among the spectrum of perimenopausal uterine alterations, it is important to include endometrial hyperplasia, a condition that is characterised by morphological alterations in the ratio of endometrial glands/stroma.[18] This disease frequently occurs after forties and the risks cannot be underestimated.

There are several conditions related to the perimenopause that could benefit from the use of modern contraceptives, mainly hormonal, with the goals of avoiding unintended pregnancies and providing further benefits beyond contraception. Fertility awareness-based methods are unreliable during the perimenopause because of unpredictable ovulation and cycles, as described above; therefore, they should not be utilised during this time. We will therefore detail the contraceptive options available to women over 40 and, also, the unique contraceptive and non-contraceptive benefits and health risks associated with different contraceptive methods in this population. Indeed, contraceptive use has recently been found to be relatively stable over time, with short-acting hormonal contraception and condoms being the most

common contraceptive methods until women reach the age of 40–45 years when long-acting reversible contraceptives (LARCs) and permanent contraception become the most prevalent.[19]

In general, according to the International Medical Eligibility Criteria for Contraceptive Use, there is no single contraceptive choice contraindicated based on age alone[20] because there is no evidence to suggest that age itself is a risk factor for contraceptive-related complications. However, with age comes an increased risk of some medical conditions, including obesity, hypertension, diabetes, hyperlipidaemia and cancer, which have to be considered as independent risk factors.

The aim of this narrative review is to give practical guidance on their possible use in this particular life stage, by separately describing Short- and Long-Acting Reversible Contraceptives (SARCs and LARCs, respectively) and to assist clinicians for women transitioning from contraception to their menopausal years, including the possible initiation of postmenopausal hormone therapy (HT). Comprehensive contraceptive counselling is an essential aspect of the overall health and wellbeing of women and should be addressed with each such patient irrespective of age. A practical guide to this particular medical counselling is reported in Box 1.

Box 1 Practical Guidance for Contraception Use in Perimenopause

SARCs

Combined Oral Contraceptive (COC)

- All doses of COCs are still appropriate for use in all otherwise healthy, perimenopausal women.
- Check the WHO Guidelines[19] for eligibility (excluding smoking, hypertension, migraine, systemic lupus erythematosus with antiphospholipid antibodies, thrombosis history, known thrombogenic mutations, etc.).
- Possible use in Virgo women.
- Prefer products containing estradiol (quadriphasic estradiol valerate/dienogest, monophasic estradiol/nomegestrol acetate), in particular as the first CHC prescription.[40,42,43]

Possible extra-contraceptive benefits

- Menstrual cycle control.
- Reduction of primary/secondary dysmenorrhea.
- Treatment of women with endometriosis.[95]
- Reduction of vasomotor symptoms, such as hormone-related headaches or menstrual migraines.
- Protection of bone health.
- Reduction of endometrial, colorectal and ovarian cancer risk.

Vaginal Ring

- Check the WHO Guidelines[19] for eligibility (excluding smoking, hypertension, migraine, systemic lupus erythematosus with antiphospholipid antibodies, thrombosis history, known thrombogenic mutations, etc.).
- Consider in women who desire to avoid daily pill intake/forgetful.

Possible extra-contraceptive benefits

- Menstrual cycle control.
- Reduction of primary/secondary dysmenorrhea.
- Treatment of women with endometriosis.[95]
- Reduction of vasomotor symptoms, such as hormone-related headaches or menstrual migraines.
- Protection of bone health.
- Improvement in vaginal lubrication.
- Improvement in lactobacillus species in vaginal flora.[96]

Patch

- Check the WHO Guidelines[19] for eligibility (excluding smoking, hypertension, migraine, systemic lupus erythematosus with antiphospholipid antibodies, thrombosis history, known thrombogenic mutations, etc.).
- Possible use in Virgo women.
- Consider in women who desire to avoid daily intake/forgetful.
- Its use in this age group is infrequent/not preferable (higher estrogen levels).[97]

Possible extra-contraceptive benefits

- Menstrual cycle control.
- Reduction of primary/secondary dysmenorrhea.

(*Continued*)

Box 1 (Continued).

- Treatment of women with endometriosis.[95]
- Reduction of vasomotor symptoms, such as hormone-related headaches or menstrual migraines.
- Protection of bone health.

Progestin-only pill (POP)

- Check the WHO Guidelines[19] for eligibility (excluding personal history of active or recent (within 5 years) breast cancer or lupus erythematosus with positive or unknown antiphospholipid antibodies, etc.).
- Possible use in Virgo women.
- Consider in women with a contraindication to oestrogens.

Possible extra-contraceptive benefits

- Menstrual cycle control (unpredictable, possible amenorrhea).
- Reduction of primary/secondary dysmenorrhea.
- Treatment of women with endometriosis.[95]
- Possible reduction of menstrual migraines.

LARCs

- **Cu-IUD**
- Check the WHO Guidelines[19] for eligibility (excluding distorted uterine cavity, current pelvic inflammatory disease, purulent cervicitis, chlamydial infection or gonorrhoea, Wilson syndrome, etc.).
- Avoid in women with heavy menstrual bleeding.
- Consider in women who should avoid exposure to hormones, eg, [hormone fears and misconceptions or with contraindications to oestrogen and progestin assumption (eg, breast cancer survivors)].

Possible extra-contraceptive benefits

- Reduction of endometrial, cervical and ovarian cancer risk.
- Possible use as an emergency contraceptive.

Implant

- Check the WHO Guidelines[19] for eligibility [exclude personal history of active or recent (within 5 years) breast cancer or lupus erythematosus with positive or unknown antiphospholipid antibodies, etc.].
- Possible use in Virgo women who desire LARC use.
- Consider in women with BMI >30 and metabolic diseases.
- Consider in women with contraindication of oestrogens.

Possible extra-contraceptive benefits

- Menstrual cycle control (unpredictable/possible amenorrhea).
- Reduction of primary/secondary dysmenorrhea.
- Treatment of women with endometriosis.[95]

Depot medroxyprogesterone acetate (DMPA)

- Check the WHO Guidelines[19] for eligibility (excluding personal history of active or recent (within 5 years) breast cancer or lupus erythematosus with positive or unknown antiphospholipid antibodies, etc.).
- Possible use in Virgo women
- Its use in this age group is infrequent/not preferable (negative effect on bone health).[65]

LNG-IUS

- Check the WHO Guidelines[19] for eligibility (excluding personal history of active or recent (within 5 years) breast cancer or lupus erythematosus with positive or unknown antiphospholipid antibodies, distorted uterine cavities, etc.).
- Consider in women with a contraindication to oestrogens

Possible extra-contraceptive benefits

- Menstrual cycle control.
- Reduction of primary/secondary dysmenorrhea.
- Treatment of women with endometriosis.[95]
- Treatment of abnormal uterine bleeding without an organic cause (on-label).
- Treatment of women with fibroids (not distorting the endometrial cavity) and adenomyosis (off-label).
- Prevention/treatment of endometrial polyps.
- Prevention/treatment of endometrial hyperplasia/endometrial intraepithelial neoplasia.
- Possible use as a progestin component for postmenopausal hormone therapy (on-label).
- Reduction of endometrial, cervical and ovarian cancer risk.

Short-Acting Reversible Contraceptives (SARCs)

Combined Hormonal Contraceptives (CHCs)

CHCs are available as a daily pill [combined oral contraceptives (COCs)], a weekly transdermal patch, a monthly vaginal ring (three weeks of use) and in few countries (US, Latin America) some monthly injectable combined contraceptives. These methods are made with an estrogenic component ("combined"), such as ethinyl-oestradiol (EE), E2, a natural oestrogen and, more recently, oestetrol (E4), in combination with many progestins, which can be derived from natural progesterone, from 19 nor-testosterone or by spironolactone.[21]

The general mechanism of action of these contraceptives is to inhibit ovulation, stabilise endometrial proliferation and modify the cervical mucus in order to make it inhospitable for the ascent of spermatozoa.[22] CHCs are highly effective when correctly used, but they are prone to a higher risk of user failure due to the necessity of regular intake, so there is a significant difference between ideal use and typical use for contraceptive effectiveness. Perfect use failure rate is 0.3% and typical use failure rate is up to 7–9% in reproductive-age women. However, this difference is not as high in perimenopausal women compared to younger women due to the physiological decline of natural fertility.[23] In the last 60 years, important developments in CHC technologies have been achieved, guaranteeing women more choices than in the past while maintaining/improving contraceptive efficacy: nowadays, new formulations of CHCs are available on the market with very low oestrogen doses as well as natural oestrogens (E2 and E4) and progestins without many of the androgenic side effects.[21]

A recent meta-analysis of 18 RCTs comparing the patch, ring and COCs found no significant differences in contraceptive effectiveness, indications and contraindications between the different SARCs.[24]

For women in perimenopause, CHC use offers, beyond a valid contraceptive method, potential additional benefits such as:

- satisfactory menstrual control, which avoids AUB, resulting in regular menstrual bleeds and further reducing dysmenorrhea and pelvic pain.[25]
- A reduction of vasomotor symptoms, such as hormone-related headaches or menstrual migraines, which occur in more than 60% of perimenopausal women, especially during a hormone-free interval (HFI).[17,25,26]
- Protection against bone loss via two mechanisms: preventing bone demineralisation, which is very important in this life-stage, and enhancing bone mineral density, even at low doses.[27]
- A reduction of endometrial, colorectal and ovarian cancer risk, close to their peak incidence.[28]

Overall, CHCs are still appropriate for use in all otherwise healthy, perimenopausal women.

The advantages of CHCs use in comparison to progestin-only contraceptives use are reported in Figure 2.

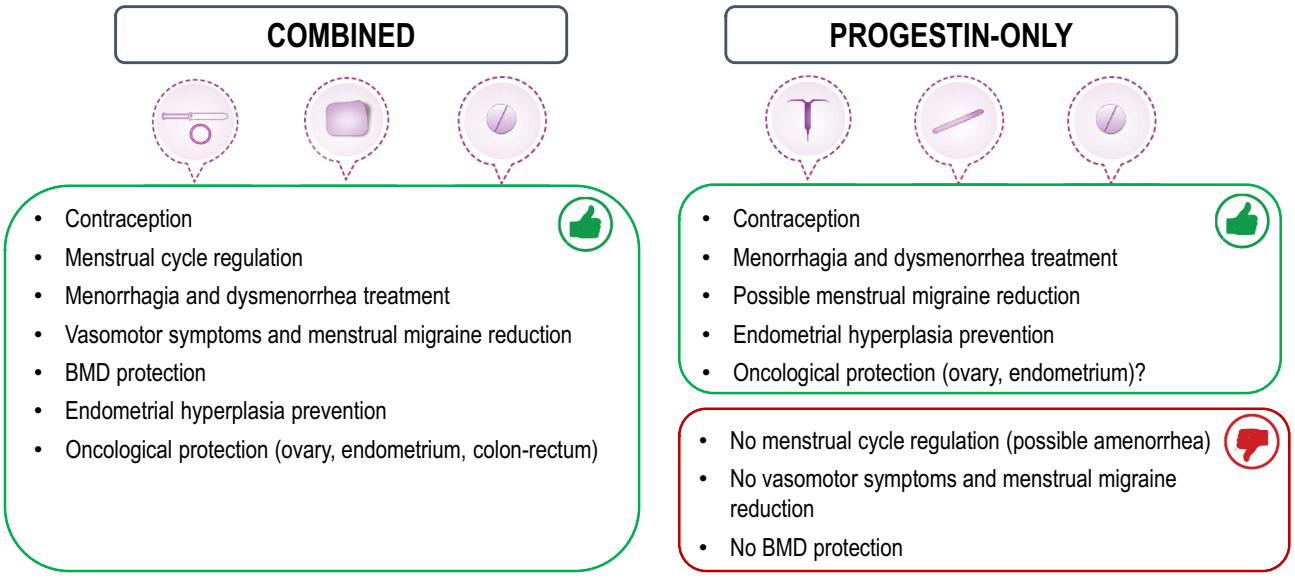

Figure 2 Pros and cons of the use of combined hormonal contraceptives (CHCs) or progestin-only contraceptives in the perimenopause.

COCs

COCs are the most commonly used hormonal contraceptives worldwide and remain a valid option thanks to their flexibility, convenience and well-known non-contraceptive benefits. COCs are available in:

- cyclic regimens, composed of 21 active pills and 7 inactive pills/no assumption
- a shortened HFI regimen, composed of 24–26 active pills and 2–4 inactive pills
- an extended regimen, which includes 84 active pills and 7 inactive pills
- a continuous regimen, which is made up of a 365 active pill regimen

The shorter the scheduled menstrual interval is, the less vasomotor effects, menstrual migraine and abnormal menstrual bleeding shall occur. Clinical experience shows that the continuous use of all types of COCs is effective in reducing blood loss.[29] This reduction also seems to be influenced by the dosage of EE; in fact, it is greater with 30–35 μg compared to 20 μg[30] and the type of oestrogen administered. Recent studies have demonstrated that even COCs with E2 seem to act very effectively in the management of heavy menstrual bleeding (HMB). In particular, it has been seen that the quadriphasic combination of oestradiol valerate (E2V) and dienogest has an important effect in reducing HMB, with a reduction of between 80 and 120 mL of blood per menstrual cycle.[31]

COCs, Vasomotor Symptoms and Menstrual Migraine

There is some evidence about the role of CHCs to also improve vasomotor symptoms: hot flushes could already appear in the premenopausal period and are effectively reduced by CHC use. For women who have already experienced the first symptoms of menopause during this period, COC therapy appears to be a more accepted option than postmenopausal hormone therapy (HT). One study evaluated COCs with an alternative option for oestrogen exposure during the usual placebo week: one group received 10 μg of EE for 5 days with 2 days of placebo and the other group received traditional placebo pills for 7 days. All women reported a decrease in somatic, anxiety and depression symptoms. In the group treated with additional oestrogen, there was an even larger decrease in vasomotor symptoms, depression, somatic symptoms and sexual dysfunction compared with those who received placebo during the hormone-free week.[32]

During perimenopause, migraine frequency and severity increase, particularly in women with menstrual migraine. This may partly be because menstruation and consequently menstrual migraine are more frequent as the cycle length shortens. Women with migraine also have a significantly increased risk of vasomotor symptoms, anxiety and depression, as well as sleep disturbance, further increasing morbidity. On the contrary, post-menopause, the prevalence of migraine without aura declines. In contrast, migraine with aura is not directly affected by menopause and headache becomes less of a feature of attacks with increasing age.[33] In theory, continuous COC use, which suppresses ovarian activity as well as menstrual bleeding, should effectively manage hormonal migraine triggers. However, there are only limited clinical trial data regarding migraine. The European Headache Federation (EHF) and the European Society of Contraception and Reproductive Health (ESCRH) recommend COCs for women with migraine who require contraception, experience oestrogen-withdrawal headaches, or benefit from treatment with COCs for medical reasons.[34] In all cases, continuous use is advised to prevent oestrogen-withdrawal migraine triggered during breaks. If breaks are necessary to control unscheduled bleeding, they should be shortened to four days. CHCs can be used by women with migraine without aura but are contraindicated for contraceptive use in women with migraine with aura since both COCs and aura are independent risk factors for ischemic stroke.

COCs and Bone Mineral Density

There are still no reliable data in the literature about the effect of COC on bone mineral density (BMD): in general, CHC use does not seem to exert any significant, nor detrimental or protective, effect on bone in the general population.[35] While the strongest beneficial effect of CHCs on BMD was seen in perimenopausal women with low oestrogen levels, it is still not clear whether this effect might mitigate fracture risk.[27]

COCs and Cardiovascular Risk

The relative risk of thromboembolic diseases increases slightly in COC users, which is about two to three times higher than in non-users. However, the greatest risk occurs within the first 3 months of initiation (OR 12, 95% CI 7.1–22.4).[36] The incidence of VTE sharply increases after age 40, thus demonstrating that age plays an important role. A meaningful Danish cohort study found that the incidence of VTE in COC users rose from 8.7 per 10000 women-years for women aged 30–34 to 20.8 per 10000 women-years for women aged 45–49.[37] Another large case–control study found that the incidence rate of VTE in COC users increased by nearly 3-fold between the ages 20–29 and over 40.[38] The risk of VTE in patients using COCs is influenced by both the type of progestin and the dose of oestrogen contained. A study performed by Sugiura et al shows that COCs with 20 μg of EE have a lower risk of pulmonary embolism and serious arterial thromboembolic events than COCs with 30–40 μg EE. In addition, using COC-containing levonorgestrel (LNG) is associated with a 50% lower risk of pulmonary embolism (PE) compared with using a COC with a third-generation progestin.[39] The absolute risk of thrombotic stroke (TS) and myocardial infarction (MI) associated with COC is low in women of reproductive age but increases with age, EE dose and the presence of additional cardiovascular risk factors such as smoking, hypertension, diabetes, obesity and hyperlipidaemia.[7] However, during counselling, the increased maternal morbidity and mortality of pregnancy related to older age should be addressed, including the fact that any particular contraindication of hormonal contraceptives also increases the risk of significant adverse events during pregnancy.

The incidence of TS and myocardial infarction (MI) was 20- and 100-times higher in an older cohort (aged 45–49 years) versus a younger cohort (aged 15–19 years) of Danish women, respectively; also, considering COC use, the overall risk of stroke increases by 2.2-times and that of MI by 2.3-times.[37] A significantly increased risk of TS in women who use CHCs was also shown in a Cochrane review[40] including 24 observational studies. The dose of EE seems to influence the risk of TS and MI. The Cochrane review found the relative risk of stroke and MI to increase from 1.6 (95% CI 1.4–1.8) for 20 μg EE to 2.0 (95% CI 1.4–3.0) for 30–50 μg EE; also, the Danish study had comparable, but non-significant findings, with an RR of 1.6–1.9 for current COC use depending on EE dose.[37]

In recent years, COCs containing E2 rather than EE have been developed.[41] The most important exponents are a quadriphasic preparation containing E2V+dienogest (DNG) and a monophasic preparation containing micronised E2 +nomegestrol acetate (NOMAc). Both have a short HFI, which results in better menstrual cycle control. It seems that using an estrogenic component identical to the natural one might offer a safer alternative to the traditional pill containing EE. These preparations share some similarities with postmenopausal HT preparations, rather than COCs, and so have theoretical safety benefits for women over 40. However, there is currently insufficient evidence to define a specific recommendation for the use of these preparations in women over 40. Preparations containing natural E2 seem to be more neutral than those with EE due to their theoretical safety benefits for women over 40 years of age; in the Expert Opinion of the authors, these are clearly the first-line choice between different CHCs in these women, especially if non-oral methods of E2 administration will be soon available.[42]

Noteworthy, WHO eligibility criteria do not report differences between E2 and EE-containing products,[19] but, it is assumed that there could be a risk difference between diverse oestrogen components (EE versus E2). The INAS SCORE study by Dinger et al shows that COC containing E2V and DNG is associated with a similar or even lower cardiovascular risk compared to COCs containing LNG or other progestins.[43] A similar recent large post-marketing study that includes a total of 101,498 women, with 49,598 using E2-NOMAc and 51,900 using EE-LNG for up to 2 years, has found a risk of VTE and PE in NOMAc-E2 which is similar to or even lower than that of LNG-based COCs users [HR adjusted of 0.59 (95% CI 0.25–1.35) (adjusted for age, BMI, family history of VTE and current duration of use)].[44]

COCs and Oncological Risk

The RR of both ovarian cancer and endometrial cancer is significantly reduced when using COCs; this protective effect increases with the duration of therapy and remains several decades after its interruption. A systematic review shows that the risk of ovarian cancer is reduced by at least 50% with COC use (<40 μg EE)[45] and another collaborative reanalysis of

45 epidemiological studies found a 20% reduction in ovarian cancer risk for every 5 years of COC use.[46] This effect was more evident if COCs have been used near the peak of incidence of ovarian cancer, precisely the perimenopause.[45]

For these reasons, COCs could be used as a chemoprophylactic strategy for younger women with a BRCA1 or BRCA2 gene mutation.[47] Observational studies have also shown a reduction in functional ovarian cysts and benign ovarian tumours development in COC users,[48] which are very common in this life stage.

The risk reduction for endometrial cancer is between 50% and 70%; in particular, the risk reduction in endometrial and serous serotypes is greater than in the mucinous one.[49] In women using COCs for at least 12 months, the protection could last for at least 15 years after discontinuation.[50]

There is little evidence regarding CHC use and breast cancer risk, related specifically to women aged over 40. The increased risk is basically age-related: if the risk of developing breast cancer at 35 years is 1/500, it is 1/100 at 40.[51] Studies with older COC formulations (higher-dose) found a slightly increased risk of breast cancer (with RR in the range 1.24–1.30) that declines gradually after cessation, with no significant risk of breast cancer after 10 years of non-use.[28] However, nowadays, with the use of low-dose pills, this risk does not seem to exist or to be minimal at most: one meta-analysis of five cohort studies found a very small but significant increase in breast cancer risk for every 5 (RR 1.07, 95% CI 1.03–1.11) and 10 (RR 1.14, 95% CI 1.05–1.23) years of use.[51]

In the Danish study, the RR of developing breast cancer for recent and current users of any hormonal contraceptive (mostly utilising COCs) is 1.20 (95% CI 1.14–1.26, p = 0.002). This means one extra breast cancer per 7690 women using a CHC for one year.[52] Importantly, the study has some limitations regarding other important confounding factors for breast cancer risk: in particular, the BMI is not known for all patients while breastfeeding, family history or other oncological risks were not included in the analysis.

For BRCA1/BRCA2 carriers, who themselves have an increased baseline risk, there does not appear to be an additional risk associated with COC use.[53]

It is important to take in mind that the specific benefits/risks ratio according to these specific topics (cardiovascular and oncological risk) can additionally change between different ages of reproductive years and between starters and long-term COC users:[51] then, counselling should be personalised.[11] Some risks differ if COC use begins in middle age or if use is continued from a young age. The thrombotic risk increases with age and is greatest in the first months of use. Additionally, the presence of other cardiovascular risk factors (eg, obesity, smoking, hypertension, and diabetes) highlights the importance of eligibility criteria and may even contraindicate the use of COC. On the other hand, the risk of cervical cancer should increase after continuous use for more than five years in women with human papillomavirus, while data about the cumulative risk of breast cancer data are conflicting.[54]

Vaginal Ring

The contraceptive ring is a type of CHC that does not involve a daily intake. It can be used cyclically (in for 3 weeks, out for 1 week) or continuously (in for four weeks, replaced immediately with a new ring) which is a way to avoid the oestrogen-withdrawal symptoms experienced by perimenopausal women while maintaining contraceptive efficacy.[55,56]

In the literature, studies comparing the ring and COCs showed fewer reports of nausea, acne, irritability and depression in ring users, but more complaints of vaginitis and genital itching.[24] On the other hand, with regard to uterine bleeding patterns, there are conflicting data: some studies report less abundant cycles and spotting with the ring, while others do not. Concerning the cardiovascular risk, not enough events of TVE, stroke or MI have been found to assess the differential risk in comparison to COCs.[57]

This system has the important pros of a better vaginal lubrication thanks to local oestrogen which is very important in this life stage in which many women begin to suffer from vulvovaginal atrophy: 98% of women showed good lubrication after just 3 cycles of treatment. This is associated with a favourable impact on vaginal flora (increase in lactobacilli) and a perfect cycle control, superimposable/superior to that of a COC containing EE 30 μg.[58]

Transdermal Patch

The contraceptive patch is, like the vaginal ring, a type of CHC that does not demand daily attention: it is applied to the skin and worn for 7 days to suppress ovulation, after which the patch is replaced on a weekly basis for two further weeks. The fourth week is patch-free to allow a withdrawal bleeding.

Its use in this age group is infrequent, and there are no definite data on its continued use; as mentioned earlier in perimenopause, this is preferred to avoid the occurrence of symptoms in the window period. However, according to the International Medical Eligibility Criteria for Contraceptive Use, there are no contraindications on the use of transdermal patch in this life stage.[19] However, few studies showed that patch users were less likely to experience bleeding and spotting than COC users but were more likely to report breast discomfort, nausea, vomiting and menstrual pain.[24]

With regard to cardiovascular risk, there seems to be an increased risk of VTE with the contraceptive patch compared to COCs in some studies. If we add to the aforementioned absence of long-term safety data, this contraceptive is definitely not the first line for the perimenopausal woman.[59]

Progestin-Only Pill (POP)

Progestin-only pills (POPs), are oestrogen-free oral contraceptives containing only synthetic progestins in low doses, even lower than those of combined pills. Most perimenopausal patients with contraindications to oestrogen-containing options, including tobacco use, obesity, migraines with aura, long-standing diabetes, hypertension, or a history of venous thromboembolism (VTE), can safely use POPs. Contraindications to POPs are limited to a personal history of active or recent (within 5 years) breast cancer. Their mechanism of action involves changes in cervical mucus, endometrial development, corpus luteum function and tubal motility and sometimes also prevention of ovulation.[60,61] Administration is daily and continuous, without breaks. Most of the commonly used preparations contain LNG (30 µg), norethisterone (350 µg) and desogestrel (75 µg). The type of progestin that has the greatest efficacy on ovulation inhibition is desogestrel, which is comparable to that of CHCs.[62] With the decline in fertility with age, the traditional POP becomes increasingly effective in older users.[10] A new option for a POP was recently released with a product containing 4 mg of drospirenone (DRSP): it suppresses ovulation and thickens cervical mucus because of its higher doses of progestin. This allows more leeway in the dosing schedule and maintains effectiveness, even with a missed or late pill. DRSP has strong anti-mineralocorticoid and antiandrogenic properties. The anti-mineralocorticoid properties may lower blood pressure and reduce fluid retention, helping to combat bloating and some of the weight changes observed in perimenopause. The antiandrogenic properties have been shown to have a better impact on arterial cardiovascular risk.[21]

The use of DRSP-only pills showed higher rates of scheduled bleedings and amenorrhea rates and much lower rates of unscheduled intracyclic bleeding/spotting in comparison to continuous desogestrel regimen of POP.[20]

The use of POPs may be beneficial in this age group because of the lack of association they have with VTE, stroke, or MI.

The risk of breast cancer in users of POPs is controversial: in some studies, the risk appears to be the same as for CHCs, while there is no increased risk in others. Nevertheless, if there is also an increase in risk, it remains minimal and will continue to reduce after the cessation of POPs.[61] On the other hand, with regard to its action on bone, there is no evidence in the literature of a negative effect on BMD.[35]

In contrast, the impact on bleeding patterns is important: they are altered in 50% of women using this type of contraceptive. The bleeding rates associated with DRSP-only pill are better than those for the DSG 75 µg POP, which are reported to be around 20% for scheduled withdrawal bleeding, 60% for unscheduled intracyclic bleeding/spotting and 15% for amenorrhoea.[63] Thus, the DRSP-only pill shows higher rates of scheduled bleedings and much lower rates of unscheduled intracyclic bleeding/spotting. The improved predictability of bleeding with the DRSP-only pill is an important advantage of this new hormonal contraceptive.

Depot Medroxyprogesterone Acetate (DMPA)

DMPA is an injectable contraceptive whose effects last for three months, and which contains 104–400 mg of medroxyprogesterone acetate.[5] There are not enough eligible data about its use during perimenopause due to its limited use in

some countries. DMPA is related to a small loss in bone mineral density that is generally regained after cessation; however, it could reduce bone density that represents a critical factor that occurs physiologically during the climacteric period. Therefore, it is not a first-line contraceptive method after the age of 45 years, although there are no formal contraindications.[64] The dose of DMPA is relatively high compared with the progestin doses in other progestin-only and oestrogen-containing contraceptive methods, with several unique implications for its use. Of the benefits, amenorrhea rates are higher than other methods – up to 50% at 1 year of use, with the prevalence of amenorrhea further increasing with ongoing use. The relatively higher dose of progestin prevents clinically significant interactions with medications that induce liver enzymes and can attenuate the contraceptive efficacy of the implant and COCs. However, a return to fertility can be delayed by up to an average of 10 months after the last injection in patients who want to become pregnant after use.

LARCs

LARCs can represent methods based on mechanical inflammatory effects or progestin-only administration, so that they do not provide any risk of cardiovascular disease or stroke and none of the other risks and contraindications related to oestrogen use or simple mechanical methods. These include levonorgestrel-releasing intrauterine systems (LNG-IUS), etonogestrel subdermal implants and copper intrauterine devices (Cu-IUDs).

Cu-IUDs

Cu-IUDs are a non-hormonal contraceptive method that creates an endometrial inflammatory response causing oedema, an increase in vascular permeability and macrophage infiltration that creates an unfavourable environment for the embryo implant. The copper ions released in utero are spermicidal. Thanks to its long action (between 5 and 12 years)[65] it can be an ideal contraceptive method during the whole climacteric, especially in women with contraindications to hormone supplementation.[49] No evidence that the Cu-IUDs lose its effectiveness after 10 years of use has been found at this life stage.[66]

Another advantage is that Cu-IUDs can provide emergency contraception if the insertion is within 5 days of unprotected sexual intercourse.[67]

Contraindications to IUD placement include the following: known or suspected pregnancy, known or suspected pelvic inflammatory disease, known or suspected pelvic malignancy, or anatomic conditions that prevent proper placement. IUDs can easily be placed in an office or clinical setting, without the need for anaesthesia in most instances. The cumulative risk of IUD expulsion is 10% over 3 years of use. Satisfaction and continuation rates associated with the use of IUDs are significantly higher than those associated with the use of SARCs such as COCs.

Additionally, Felix et al demonstrated a protective effect on the risk of endometrial cancer compared with women without these devices.[68] However, their use is not recommended in women with heavy menstrual bleeding or dysmenorrhea, because copper intrauterine devices can accentuate these two problems; the bleeding patterns can also occur in women without abnormal endometrial bleeding, but these are not harmful and decrease overtime.[7] As we can see, Cu-IUDs do not act on climacteric symptoms and cannot be used in women with a dysmorphic uterus or known pelvic inflammatory disease, or in women with submucous fibroids distorting the uterine cavity.[7] Finally, when introducing a Cu-IUD, the woman has to be aware of the risks (very rare) of the procedure, including uterine perforation (2/1000), infections in the first 20 days (<1/300) and dislocation (5%).[49]

Implant

Various types of subdermal implants are available worldwide with the 68 mg etonogestrel (Nexplanon® or Implanon NXT®) being the most common. It is a subdermal implant which releases etonogestrel only and it has to be inserted and removed by trained operators and in a specific body area, which is 8–10 cm above the medial epicondyle of humerus. It has a contraceptive efficacy higher than tubal sterilisation with a Pearl index = 0.05/100 women-years. Its pharmacokinetics are such that there is a peak of 220 pg/mL of etonogestrel within the first 4 days after its implantation, which is greatly higher than the minimum dose needed to inhibit ovulation (90 pg/mL).[69] By stopping the ovarian activity, ESI can act on endometriosis and other conditions affected by hormonal changes.[70] The only real discomfort caused by ESI is the

unpredictability of the bleeding pattern[71]: for this reason, 15% of women require its removal, as demonstrated by a US study;[72] other reviews count prolonged/frequent bleeding in approximately one in five women.[73] There are no associations with the loss of bone density or metabolic effect[74], and it is recommended in obese women as well.[75] To underline these data, women with BMI >30 kg/m^2 generally do not require its removal[72] and have an optimal hormonal distribution, unlike other contraceptive methods in which metabolism is highly influenced by weight. ESIs have to be replaced 3 years after implantation and, unlike IUDs, there are no recommendations to retain them for longer during the perimenopausal period.[74] There is no specific action on the endometrium, so it appears that implants do not protect against endometrial hyperplasia and breast cancer is a contraindication to its use.[49] Based on the aspects discussed here, the perfect phenotype for ESI in climacteric includes women with BMI > 30 kg/m2 and metabolic diseases or with a contraindication to oestrogen use.

LNG-IUS (Levonorgestrel-Releasing Intrauterine System)

This is an intrauterine device that releases levonorgestrel only; it is available in three different dosages (13.5 mg, 19.5 mg and 52 mg), all of them approved for contraceptive use throughout reproductive life. However, only the one which contains 52 mg of LNG has proven its effectiveness as an endometrial protection if estrogen replacement therapy is provided.[76] LNG-IUS insertion has few contraindications and lots of benefits during climacteric and, if inserted after 45 years, it can be retained for up to seven years in women with menstrual disorders or until menopause if amenorrhoeic (off-label).[49] Within those 7 years, LNG-IUS 52 mg safely prevents pregnancy (contraceptive failure rates are 0.1% per year in typical use): as a matter of fact, it causes endometrial suppression and increases cervical mucus.[6] The IUS has one of the lowest failure rates of all contraceptive options (0.1% typical and perfect use failure rate).

LNG-IUS has been demonstrated to be the most effective method against abnormal uterine bleeding (AUB) thanks to its ability to decrease endometrial growth and prostaglandin ratio by promoting the formation of arachidonic acid in the endometrium.[6] LNG-IUS is a safe and effective option in women in perimenopause suffering from heavy bleeding caused by benign lesions in the uterus or dysmenorrhea.[77] In another study, the efficacy of LNG-IUS was compared with medroxyprogesterone acetate and continuous oral progestin assumption, with the evidence of the supremacy of the first method in reducing heavy menstrual bleeding in perimenopausal women.[78] Therefore, LNG-IUS 52 mg has to be considered the first-line method in reducing excessive bleeding in women in their forties, considering that amenorrhoea is expected in up to 45% of women within 6 months of insertion and in up to 50% of women within one year.[79] Perimenopausal patients with HMB experience reductions in menstrual bleeding similar to endometrial ablation, often precluding the need for surgery.[80]

As stated before, the risk of endometrial cancer increases during perimenopause and the rate of endometrial hyperplasia consequently rises. LNG-IUS has showed a concrete efficacy in reducing typical endometrial hyperplasia, so it is recommended in recent guidelines to be the first-line method in this treatment. A study conducted by Abu Hashim et al[81] showed endometrial atrophy after 24 months of LNG-IUS insertion in 100% of women with a documented typical endometrial hyperplasia.[6]

The treatment with LNG-IUS 52 mg has also been used in the case of hyperplasia with atypia (endometrial intraepithelial neoplasia), and it has been associated with its significant regression (moderate-quality evidence) compared with no treatment.[82]

Moreover, few studies of its use also in the case of early-stage endometrial cancer stage I A1 in women who want to preserve fertility have been published, with or without an associated systemic progestin therapy, but its feasibility/effectiveness has to be clearly demonstrated.

LNG-IUS combined with progesterone ameliorates endometrial thickness and pregnancy outcomes of patients with early-stage endometrial cancer or atypical hyperplasia.[83,84]

Another indication to LNG-IUS 52 mg use is the presence of symptomatic fibroids, unless they are submucosal, because they could cause difficulties in the insertion of LNG-IUS due to endometrial inhomogeneity.[6] Generally, myomas tends to reduce in menopause, but there are cases in which they provoke abnormal bleeding difficult to control; in addition, fibroids induce aromatase expression, determining the production of inflammatory markers in the endometrium.[85] In those cases, the use of LNG-IUSs should be taken into account. In a study regarding the use of LNG-IUS in perimenopausal women with

uterine fibroids, hysterectomy was avoided in 89.5% of women after 24 months of LNG-IUS 52 mg insertion.[86] Finally, some oncologists consider the use of LNG-IUS in women using tamoxifen to prevent endometrial hyperplasia.[87]

Some authors have explored the association between an increase in body weight compared with other contraceptive methods. It turns out that the increase in body mass index (BMI) with LNG-IUS was higher than in the control group but lower than with the desogestrel-only pill.[88] There is a concern that LNG-IUS can increase the risk of breast cancer: there are contrasting data regarding these topics, as some articles have proven the association between LNG-IUS and breast cancer, while others report the opposite.[51] Thus, further research is needed to establish whether there is a real connection with breast cancer risk. Currently, UK Medical Eligibility Criteria for Contraceptive Use state that the risk of LNG-IUS use in women with active breast cancer is in category 4 (unacceptable risk), whereas the risk is in category 3 (risk outweigh benefits) for those women who have experienced breast cancer in the past 5 years with no active disease.[49] There is no contraindication for patients considered to be at high-risk of breast cancer (eg, family history of breast cancer or BRCA1/2 mutation carriers).

Moreover, LNG-IUS 52 mg has been well studied in combination with oestrogens and is approved for use as HT outside of the United States.[89,90,91] Although the IUS has contraceptive efficacy for longer than 5 years, it may not provide adequate endometrial protection from hyperplasia after this time, particularly the IUS with the lower doses IUS.[76] Therefore, women using a lower dose of IUS should be counselled with regard to changing the device earlier to ensure adequate endometrial protection while using HT.

Ultimately, it seems that LNG-IUS can be associated with important mood changes in a smaller group of vulnerable women[92] (made worse by the climacteric period itself), so that they require antidepressants and have a higher risk of hospitalisation for depression.[93]

Irreversible Contraception - Sterilisation

Permanent sterilisation, either via vasectomy of the patient's partner or tubal ligation/salpingectomy (to further prevent ovarian cancer) is another possible option in this life stage. These are highly effective methods with 0.5% failure rates or lower. Patients should be counselled that these are not reversible and are considered permanent solutions. Since there are currently even more effective and long-acting reversible methods of contraception, the use of this contraceptive method should increasingly decrease and be selected only in particular situations because it still requires surgery with the associated recovery costs and risks and it is still associated with a possible negative long-term impact on the ovarian reserve.[94]

When to Stop Contraception?

Menopause is confirmed with 12 months of amenorrhea in women ages 40 and older according to The North American Menopause Society (NAMS), while guidelines from The Faculty of Sexual and Reproductive Healthcare (FSRH) recommend two years of amenorrhea for women between 40 and 50 years old and one year of amenorrhea for those aged 50 years old or above.[7] Continue contraception therapy until menopause is recommended. NAMS further states that 90% of women will reach menopause by age 55 and recommends continuing contraception until mid-50s.[95]

If a nonhormonal contraceptive method (eg, Cu-IUD) is being used, the above amenorrhea criteria are applicable.

In the case of hormonal contraceptive use, assessing menopausal status is more challenging as amenorrhea may be artificial. Although hormonal testing is not definitive, Expert Opinion suggests that combining FSH levels with age can assist with assessing menopausal status in women using hormonal contraceptives between the ages of 50 and 55 years old.[96] Most women (95.9%) are menopausal by the age of 55 years and virtually all are menopausal by the age of 59 years.

For women using POP, implant or LNG-IUS, clinicians can check FSH levels once; if it is more than 30 IU/l, the method can be continued for one more year and then stopped (Figure 1). If the level is less than 30 IU/l, the method should be continued for another year before rechecking FSH again.[97,98] These methods can also be stopped at the age of 55 years without any hormonal evaluation (Figure 3A).[96]

For women using DMPA, FSH levels are not always impacted. In perimenopausal women, if FSH is suppressed, the levels generally return to the normal baseline prior to the next injection. For women aged 50–55 years, FSH can be checked on the day of injection and repeated 13 weeks later prior to the next injection. If both levels are more than 30 IU/l, contraception can be discontinued (Figure 3B).[65,99]

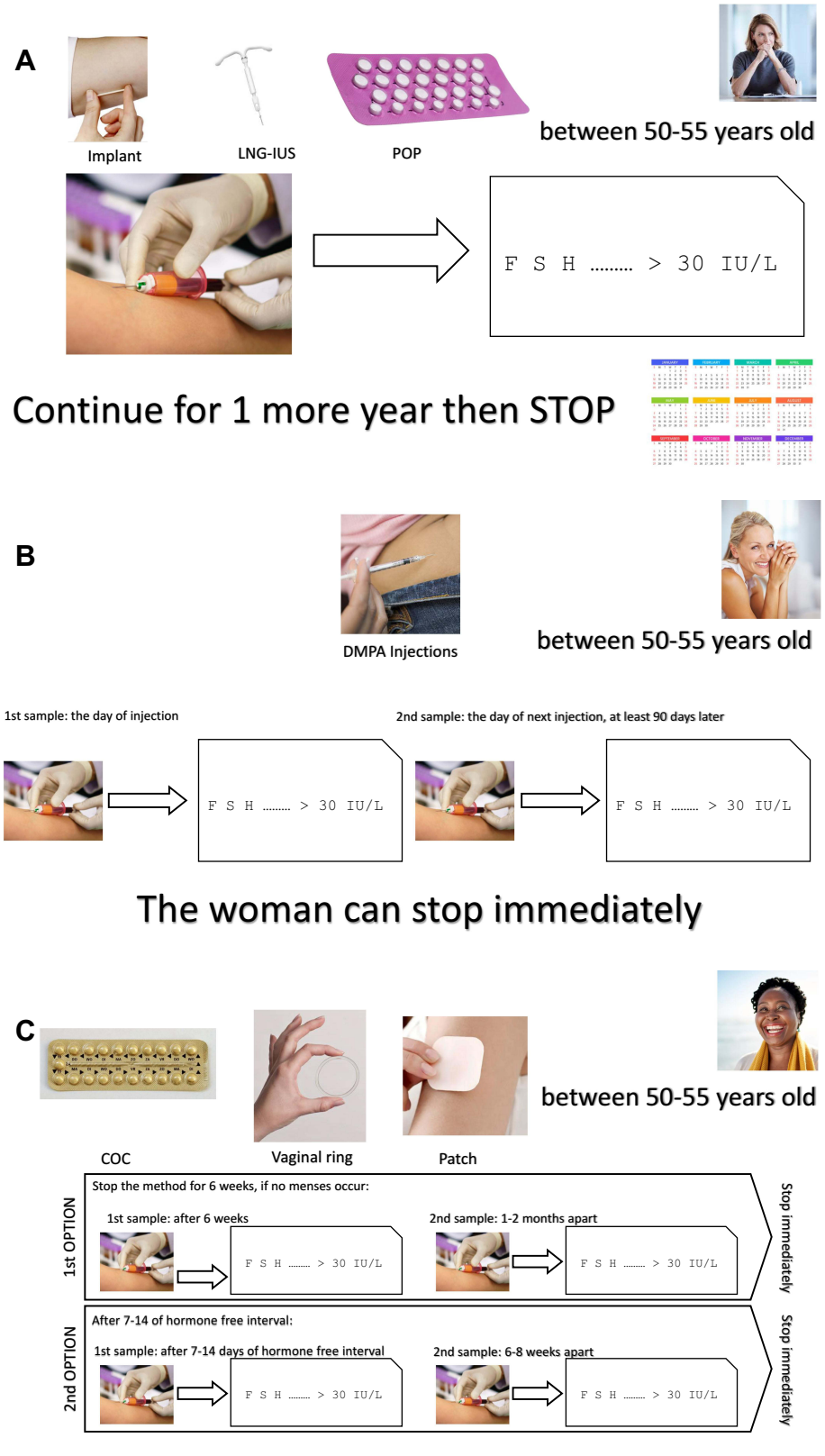

Figure 3 When to stop contraception? In the case of progestin-only pill, implant and levonorgestrel-realising intrauterine system use (**A**), depot medroxyprogesterone acetate use (**B**) and combined hormonal contraceptive (pill, vaginal ring and patch) use (**C**).

CHCs users have a more challenging scenario as FSH is more suppressed by the method. For FSRH, they should be switched to an alternative method at 50 years old (progestin-only, Cu-IUD, etc.) and then follow its specific recommendation. Another option for women aged 50 years and older is to stop their CHCs and use a non-hormonal method for a while. If they do not resume their menses after 6 weeks, they can check their FSH levels twice, 1–2 months apart; if the levels are more than 30 IU/l both times, the contraception can be stopped.[100] A second option is to check FSH levels at the end of the 7-day placebo week twice, 6–8 weeks apart. If the FSH level is more than 30 IU/l both times, contraception can be discontinued (Figure 3C).

False-negative results can occur after 7 days and may require a full 14-day hormone-free interval or longer to repeat the testing if the woman is able to use a reliable back-up method. For women on CHC, NAMS state that they may continue CHC until 55 years old if no contraindications exist (Figure 1).[95]

Once a woman discontinues CHC, she may experience the onset of menopausal symptoms, including vasomotor symptoms, sleep disturbances, vaginal and urinary tract symptoms and changes in sexual function. At this time, postmenopausal HT may be considered on an individual basis.

Acknowledgment

No particular acknowledgments for this invited review.

Disclosure

Giovanni Grandi received honoraria for sponsored lectures and participation in advisory boards from Bayer AG, Italfarmaco, Theramex, Organon, Gedeon Richter and Exeltis, not related to this manuscript. Fabio Facchinetti reports personal fees from JnJ outside the submitted work. The authors report no other potential conflicts of interest in relation to this work.

References

1. Harlow SD, Gass M, Hall JE, et al. Executive summary of the stages of reproductive aging workshop 10: addressing the unfinished agenda of staging reproductive aging. *Climacteric*. 2012;15(2):105–114. doi:10.3109/13697137.2011.650656
2. John D. *Obstetrics and Gynecology for Postgraduates*. 4th ed. Oxford: Blackwell Scientific Publications; 1986:646–676.
3. Soules MR, Sherman S, Parrott E, et al. Stages of Reproductive Aging Workshop (STRAW). *J Womens Health Gend Based Med*. 2001;10(9):843–848. doi:10.1089/152460901753285732
4. Bacon JL. The menopausal transition. *Obstet Gynecol Clin North Am*. 2017;44(2):285–296. doi:10.1016/j.ogc.2017.02.008
5. Shaaban MM. The perimenopause and contraception. *Maturitas*. 1996;23(2):181–192. doi:10.1016/0378-5122(96)83915-6
6. Joo JK, Shin JH, Lee JR, Kim MR. Levonorgestrel-releasing intrauterine system use in perimenopausal women. *J Menopausal Med*. 2021;27(2):49–57. doi:10.6118/jmm.20038
7. FSRH Clinical Guideline: Contraception for Women Aged over 40 Years (August 2017, amended September 2019). Faculty of sexual and reproductive healthcare; 2018. Available from: https://www.fsrh.org/standards-and-guidance/documents/fsrh-guidance-contraception-for-women-aged-over-40-years-2017/. Accessed July 7, 2022.
8. Chandra A, Copen CE, Stephen EH. Infertility and impaired fecundity in the United States, 1982–2010: data from the National Survey Of Family Growth. *Natl Health Stat Rep*. 2013;67:1–18.
9. Finer LB, Zolna MR. Unintended pregnancy in the United States: incidence and disparities, 2006. *Contraception*. 2011;84(5):478–485. doi:10.1016/j.contraception.2011.07.013
10. Navot D, Bergh PA, Williams MA, et al. Poor oocyte quality rather than implantation failure as a cause of age-related decline in female fertility. *Lancet Lond Engl*. 1991;337(8754):1375–1377. doi:10.1016/0140-6736(91)93060-M
11. Antinori S, Gholami GH, Versaci C, et al. Obstetric and prenatal outcome in menopausal women: a 12-year clinical study. *Reprod Biomed Online*. 2003;6(2):257–261. doi:10.1016/S1472-6483(10)61718-X
12. Grandi G, Del Savio MC, Boggio Sola V, Monari F, Melotti C, Facchinetti F. Attitudes of women towards products containing hormones (hormonal contraceptives or hormone therapy): what changes from pre to postmenopause? *Ann Med*. 2021;53(1):908–915. doi:10.1080/07853890.2021.1938662
13. Bitzer J, Platano G, Tschudin S, Alder J. Sexual counseling in elderly couples. *J Sex Med*. 2008;5(9):2027–2043. doi:10.1111/j.1743-6109.2008.00926.x
14. Speroff L, Darney PD. *A Clinical Guide for Contraception*. Lippincott Williams & Wilkins; 2011:464.
15. Munro MG, Critchley HOD, Fraser IS, FIGO Menstrual Disorders Committee; The two FIGO systems for normal and abnormal uterine bleeding symptoms and classification of causes of abnormal uterine bleeding in the reproductive years: 2018 revisions. *Int J Gynaecol Obstet off Organ Int Fed Gynaecol Obstet*. 2018;143(3):393–408. doi:10.1002/ijgo.12666
16. Davies J, Kadir RA. Heavy menstrual bleeding: an update on management. *Thromb Res*. 2017;151(Suppl 1):S70–7. doi:10.1016/S0049-3848(17)30072-5

17. Di Bella ZIK, de J Bianchi AMH, de M Araujo FF, De, Sartori MGF, Girão MJBC. Contraception and family planning at the extreme of reproductive life - climacteric. *Rev Assoc Medica Bras*. 2016;62(5):454–457. doi:10.1590/1806-9282.62.05.454
18. Sanderson PA, Critchley HOD, Williams ARW, Arends MJ, Saunders PTK. New concepts for an old problem: the diagnosis of endometrial hyperplasia. *Hum Reprod Update*. 2017;23(2):232–254. doi:10.1093/humupd/dmw042
19. Harris ML, Egan N, Forder PM, Coombe J, Loxton D. Contraceptive use among women through their later reproductive years: findings from an Australian prospective cohort study. *PLoS One*. 2021;16(8):e0255913. doi:10.1371/journal.pone.0255913
20. World Health Organization. Medical eligibility criteria for contraceptive use; 2022. Available from: https://www.who.int/publications-detail-redirect/9789241549158. Accessed July 7, 2022.
21. Chiara Del Savio M, De FR, Facchinetti F, Grandi G. Drospirenone 4 mg-only pill (DOP) in 24+4 regimen: a new option for oral contraception. *Expert Rev Clin Pharmacol*. 2020;13(7):685–694. doi:10.1080/17512433.2020.1783247
22. Rice C, Killick S, Hickling D, Coelingh Bennink H. Ovarian activity and vaginal bleeding patterns with a desogestrel-only preparation at three different doses. *Hum Reprod Oxf Engl*. 1996;11(4):737–740. doi:10.1093/oxfordjournals.humrep.a019245
23. Bitzer J. Overview of perimenopausal contraception. *Climacteric J Int Menopause Soc*. 2019;22(1):44–50. doi:10.1080/13697137.2018.1540566
24. Lopez LM, Grimes DA, Gallo MF, Stockton LL, Schulz KF. Skin patch and vaginal ring versus combined oral contraceptives for contraception. *Cochrane Database Syst Rev*. 2013;30(4):CD003552.
25. Marret H, Fauconnier A, Chabbert-Buffet N, et al. Clinical practice guidelines on menorrhagia: management of abnormal uterine bleeding before menopause. *Eur J Obstet Gynecol Reprod Biol*. 2010;152(2):133–137. doi:10.1016/j.ejogrb.2010.07.016
26. MacGregor EA. Menstrual and perimenopausal migraine: a narrative review. *Maturitas*. 2020;142:24–30. doi:10.1016/j.maturitas.2020.07.005
27. Gambacciani M, Monteleone P, Ciaponi M, Sacco A, Genazzani AR. Effects of oral contraceptives on bone mineral density. *Treat Endocrinol*. 2004;3(3):191–196. doi:10.2165/00024677-200403030-00006
28. Cibula D, Gompel A, Mueck AO, et al. Hormonal contraception and risk of cancer. *Hum Reprod Update*. 2010;16(6):631–650. doi:10.1093/humupd/dmq022
29. Long ME, Faubion SS, MacLaughlin KL, Pruthi S, Casey PM. Contraception and hormonal management in the perimenopause. *J Womens Health*. 2015;24(1):3–10. doi:10.1089/jwh.2013.4544
30. Gallo MF, Nanda K, Grimes DA, Schulz KF. 20 mcg versus >20 mcg estrogen combined oral contraceptives for contraception. *Cochrane Database Syst Rev*. 2005;18(2):CD003989.
31. Fraser IS, Parked S, Mellinger U, Machlitt A, Serrani M, Jensen J. Effective treatment of heavy and/or prolonged menstrual bleeding without organic cause: pooled analysis of two multinational, randomised, double-blind, placebo-controlled trials of oestradiol valerate and dienogest. *Eur J Contracept Reprod Health Care*. 2011;16(4):258–269. doi:10.3109/13625187.2011.591456
32. Blümel JE, Castelo-Branco C, Binfa L, Aparicio R, Mamani L. A scheme of combined oral contraceptives for women more than 40 years old. *Menopause N Y N*. 2001;8(4):286–289. doi:10.1097/00042192-200107000-00011
33. Grandi G, Imbrogno MG, Cainazzo MM, et al. Easy tools to screen Italian women suffering from migraine with and without aura in early reproductive age. *Eur J Obstet Gynecol Reprod Biol*. 2019;242:63–67. doi:10.1016/j.ejogrb.2019.09.012
34. Sacco S, Merki-Feld GS, Ægidius KL, et al. Effect of exogenous estrogens and progestogens on the course of migraine during reproductive age: a consensus statement by the European Headache Federation (EHF) and the European Society of Contraception and Reproductive Health (ESCRH). *J Headache Pain*. 2018;19(1):76. doi:10.1186/s10194-018-0896-5
35. Nappi C, Bifulco G, Tommaselli GA, Gargano V, Di Carlo C. Hormonal contraception and bone metabolism: a systematic review. *Contraception*. 2012;86(6):606–621. doi:10.1016/j.contraception.2012.04.009
36. Allen RH, Cwiak CA, Kaunitz AM. Contraception in women over 40 years of age. *CMAJ Can Med Assoc J*. 2013;185(7):565–573. doi:10.1503/cmaj.121280
37. Ø L, Nielsen LH, Skovlund CW, Skjeldestad FE, Løkkegaard E. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001–2009. *BMJ*. 2011;25(343):d6423.
38. Weill A, Dalichampt M, Raguideau F, et al. Low dose oestrogen combined oral contraception and risk of pulmonary embolism, stroke, and myocardial infarction in five million French women: cohort study. *BMJ*. 2016;10(353):i2002. doi:10.1136/bmj.i2002
39. Sugiura K, Kobayashi T, Ojima T. Risks of thromboembolism associated with hormonal contraceptives related to body mass index and aging in Japanese women. *Thromb Res*. 2016;137:11–16. doi:10.1016/j.thromres.2015.11.038
40. Roach REJ, Helmerhorst FM, Lijfering WM, Stijnen T, Algra A, Dekkers OM. Combined oral contraceptives: the risk of myocardial infarction and ischemic stroke. *Cochrane Database Syst Rev*. 2015;27(8):CD011054.
41. Grandi G, Napolitano A, Cagnacci A. Metabolic impact of combined hormonal contraceptives containing estradiol. *Expert Opin Drug Metab Toxicol*. 2016;12(7):779–787. doi:10.1080/17425255.2016.1190832
42. Grandi G, Barra F, Ferrero S, Facchinetti F. Estradiol in non-oral hormonal contraception: a 'long and winding road'. *Expert Rev Endocrinol Metab*. 2019;14(3):153–155. doi:10.1080/17446651.2019.1604217
43. Dinger J, Möhner S, Heinemann K. Combined oral contraceptives containing dienogest and estradiol valerate may carry a lower risk of venous and arterial thromboembolism compared to conventional preparations: results from the extended INAS-SCORE study. *Front Womens Health*. 2020;5(1). doi:10.15761/FWH.1000178
44. Reed S, Koro C, DiBello J, et al. Prospective controlled cohort study on the safety of a monophasic oral contraceptive containing nomegestrol acetate (2.5mg) and 17β-oestradiol (1.5mg) (PRO-E2 study): risk of venous and arterial thromboembolism. *Eur J Contracept Reprod Health Care*. 2021;26(6):439–446. doi:10.1080/13625187.2021.1987410
45. Havrilesky LJ, Moorman PG, Lowery WJ, et al. Oral contraceptive pills as primary prevention for ovarian cancer: a systematic review and meta-analysis. *Obstet Gynecol*. 2013;122(1):139–147. doi:10.1097/AOG.0b013e318291c235
46. Collaborative Group on Epidemiological Studies of Ovarian Cancer. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23 257 women with ovarian cancer and 87 303 controls. *Lancet*. 2008;371(9609):303–314. doi:10.1016/S0140-6736(08)60167-1
47. Grandi G, Sammarini M, Del Savio MC, Toss A, Facchinetti F. Combined hormonal contraceptives in BRCA gene mutation carriers: why not? *Eur J Contracept Reprod Health Care off J Eur Soc Contracept*. 2019;24(6):417–419. doi:10.1080/13625187.2019.1647335

48. Westhoff C, Britton JA, Gammon MD, Wright T, Kelsey JL. Oral contraceptive and benign ovarian tumors. *Am J Epidemiol*. 2000;152 (3):242–246. doi:10.1093/aje/152.3.242
49. UK Medical Eligibility Criteria for Contraceptive Use (UKMEC). Faculty of sexual and reproductive healthcare; 2022. Available from: https://www.fsrh.org/standards-and-guidance/uk-medical-eligibility-criteria-for-contraceptive-use-ukmec/. Accessed July 7, 2022.
50. Weiderpass E, Adami HO, Baron JA, Magnusson C, Lindgren A, Persson I. Use of oral contraceptives and endometrial cancer risk (Sweden). *Cancer Causes Control CCC*. 1999;10(4):277–284. doi:10.1023/A:1008945721786
51. Zhu H, Lei X, Feng J, Wang Y. Oral contraceptive use and risk of breast cancer: a meta-analysis of prospective cohort studies. *Eur J Contracept Reprod Health Care off J Eur Soc Contracept*. 2012;17(6):402–414. doi:10.3109/13625187.2012.715357
52. Mørch LS, Skovlund CW, Hannaford PC, Iversen L, Fielding S, Lidegaard Ø. Contemporary hormonal contraception and the risk of breast cancer. *N Engl J Med*. 2017;377(23):2228–2239. doi:10.1056/NEJMoa1700732
53. Moorman PG, Havrilesky LJ, Gierisch JM, et al. Oral contraceptives and risk of ovarian cancer and breast cancer among high-risk women: a systematic review and meta-analysis. *J Clin Oncol off J Am Soc Clin Oncol*. 2013;31(33):4188–4198. doi:10.1200/JCO.2013.48.9021
54. Mendoza N, Soto E, Sánchez-Borrego R. Do women aged over 40 need different counseling on combined hormonal contraception? *Maturitas*. 2016;87:79–83. doi:10.1016/j.maturitas.2016.02.008
55. Timmer CJ, Mulders TM. Pharmacokinetics of etonogestrel and ethinylestradiol released from a combined contraceptive vaginal ring. *Clin Pharmacokinet*. 2000;39(3):233–242. doi:10.2165/00003088-200039030-00005
56. Algorta J, Diaz M, de Benito R, et al. Pharmacokinetic bioequivalence, safety and acceptability of Ornibel®, a new polymer composition contraceptive vaginal ring (etonogestrel/ethinylestradiol 11.00/3.474 mg) compared with Nuvaring® (etonogestrel/ethinylestradiol 11.7/2.7 mg). *Eur J Contracept Reprod Health Care off J Eur Soc Contracept*. 2017;22(6):429–438. doi:10.1080/13625187.2017.1413179
57. Dinger J, Möhner S, Heinemann K. Cardiovascular risk associated with the use of an etonogestrel-containing vaginal ring. *Obstet Gynecol*. 2013;122(4):800–808. doi:10.1097/AOG.0b013e3182a5ec6b
58. Fruzzetti F, Perini D, Fornaciari L, Russo M, Bucci F, Gadducci A. Discontinuation of modern hormonal contraceptives: an Italian survey. *Eur J Contracept Reprod Health Care off J Eur Soc Contracept*. 2016;21(6):449–454. doi:10.1080/13625187.2016.1234598
59. Cole JA, Norman H, Doherty M, Walker AM. Venous thromboembolism, myocardial infarction, and stroke among transdermal contraceptive system users. *Obstet Gynecol*. 2007;109(2 Pt 1):339–346. doi:10.1097/01.AOG.0000250968.82370.04
60. Tepper NK, Whiteman MK, Marchbanks PA, James AH, Curtis KM. Progestin-only contraception and thromboembolism: a systematic review. *Contraception*. 2016;94(6):678–700. doi:10.1016/j.contraception.2016.04.014
61. Samson M, Porter N, Orekoya O, et al. Progestin and breast cancer risk: a systematic review. *Breast Cancer Res Treat*. 2016;155(1):3–12. doi:10.1007/s10549-015-3663-1
62. Endrikat J, Gerlinger C, Richard S, Rosenbaum P, Düsterberg B. Ovulation inhibition doses of progestins: a systematic review of the available literature and of marketed preparations worldwide. *Contraception*. 2011;84(6):549–557. doi:10.1016/j.contraception.2011.04.009
63. Collaborative Study Group on the Desogestrel-containing Progestogen-only Pill. A double-blind study comparing the contraceptive efficacy, acceptability and safety of two progestogen-only pills containing desogestrel 75 micrograms/day or levonorgestrel 30 micrograms/day. *Eur J Contracept Reprod Health Care off J Eur Soc Contracept*. 1998;3(4):169–178. doi:10.3109/13625189809167250
64. Petitti DB, Piaggio G, Mehta S, Cravioto MC, Meirik O, The WHO Study of Hormonal Contraception and Bone Health; Steroid hormone contraception and bone mineral density: a cross-sectional study in an international population. *Obstet Gynecol*. 2000;95(5):736–744. doi:10.1016/s0029-7844(00)00782-1
65. Miller TA, Allen RH, Kaunitz AM, Cwiak CA. Contraception for midlife women: a review. *Menopause N Y N*. 2018;25(7):817–827. doi:10.1097/GME.0000000000001073
66. Bahamondes L, Faundes A, Sobreira-Lima B, Lui-Filho JF, Pecci P, Matera S. TCu 380A IUD: a reversible permanent contraceptive method in women over 35 years of age. *Contraception*. 2005;72(5):337–341. doi:10.1016/j.contraception.2004.12.026
67. Cleland K, Zhu H, Goldstuck N, Cheng L, Trussell J. The efficacy of intrauterine devices for emergency contraception: a systematic review of 35 years of experience. *Hum Reprod Oxf Engl*. 2012;27(7):1994–2000. doi:10.1093/humrep/des140
68. Felix AS, Gaudet MM, La Vecchia C, et al. Intrauterine devices and endometrial cancer risk: a pooled analysis of the epidemiology of endometrial cancer consortium. *Int J Cancer J Int Cancer*. 2015;136(5):E410–E422. doi:10.1002/ijc.29229
69. Grandi G, Cagnacci A, Volpe A. Pharmacokinetic evaluation of desogestrel as a female contraceptive. *Expert Opin Drug Metab Toxicol*. 2014;10(1):1–10. doi:10.1517/17425255.2013.844229
70. Walch K, Unfried G, Huber J, et al. Implanon versus medroxyprogesterone acetate: effects on pain scores in patients with symptomatic endometriosis–a pilot study. *Contraception*. 2009;79(1):29–34. doi:10.1016/j.contraception.2008.07.017
71. Mansour D, Korver T, Marintcheva-Petrova M, Fraser IS. The effects of Implanon on menstrual bleeding patterns. *Eur J Contracept Reprod Health Care off J Eur Soc Contracept*. 2008;13(Suppl 1):13–28. doi:10.1080/13625180801959931
72. Casey PM, Long ME, Marnach ML, Bury JE. Bleeding related to etonogestrel subdermal implant in a US population. *Contraception*. 2011;83 (5):426–430. doi:10.1016/j.contraception.2010.09.012
73. Bateson D, McNamee K. Perimenopausal contraception: a practice-based approach. *Aust Fam Physician*. 2017;46(6):372–377.
74. Lopez LM, Grimes DA, Schulz KF, Curtis KM, Chen M. Steroidal contraceptives: effect on bone fractures in women. *Cochrane Database Syst Rev*. 2014;24(6):CD006033.
75. Xu H, Wade JA, Peipert JF, Zhao Q, Madden T, Secura GM. Contraceptive failure rates of etonogestrel subdermal implants in overweight and obese women. *Obstet Gynecol*. 2012;120(1):21–26. doi:10.1097/AOG.0b013e318259565a
76. Grandi G, Farulla A, Sileo FG, Facchinetti F. Levonorgestrel-releasing intra-uterine systems as female contraceptives. *Expert Opin Pharmacother*. 2018;19(7):677–686. doi:10.1080/14656566.2018.1462337
77. Yoo HJ, Lee MA, Ko YB, Yang JB, Kang BH, Lee KH. The efficacy of the levonorgestrel-releasing intrauterine system in perimenopausal women with menorrhagia or dysmenorrhea. *Arch Gynecol Obstet*. 2012;285(1):161–166. doi:10.1007/s00404-011-1937-3
78. Küçük T, Ertan K. Continuous oral or intramuscular medroxyprogesterone acetate versus the levonorgestrel releasing intrauterine system in the treatment of perimenopausal menorrhagia: a randomized, prospective, controlled clinical trial in female smokers. *Clin Exp Obstet Gynecol*. 2008;35(1):57–60.

79. Sangi-Haghpeykar H, Poindexter AN, Bateman L, Ditmore JR. Experiences of injectable contraceptive users in an urban setting. *Obstet Gynecol*. 1996;88(2):227–233. doi:10.1016/0029-7844(96)00194-9
80. Kaunitz AM, Meredith S, Inki P, Kubba A, Sanchez-Ramos L. Levonorgestrel-releasing intrauterine system and endometrial ablation in heavy menstrual bleeding: a systematic review and meta-analysis. *Obstet Gynecol*. 2009;113(5):1104–1116. doi:10.1097/AOG.0b013e3181a1d3ce
81. Abu Hashim H, Zayed A, Ghayaty E, El Rakhawy M. LNG-IUS treatment of non-atypical endometrial hyperplasia in perimenopausal women: a randomized controlled trial. *J Gynecol Oncol*. 2013;24(2):128–134. doi:10.3802/jgo.2013.24.2.128
82. Mittermeier T, Farrant C, Wise MR. Levonorgestrel-releasing intrauterine system for endometrial hyperplasia. *Cochrane Database Syst Rev*. 2020;9(9):CD012658. doi:10.1002/14651858.CD012658.pub2
83. Fang F, Xu H, Wu L, et al. LNG-IUS combined with progesterone ameliorates endometrial thickness and pregnancy outcomes of patients with early-stage endometrial cancer or atypical hyperplasia. *Am J Transl Res*. 2021;13(5):5412–5419.
84. Leone Roberti Maggiore U, Martinelli F, Dondi G, et al. Efficacy and fertility outcomes of levonorgestrel-releasing intra-uterine system treatment for patients with atypical complex hyperplasia or endometrial cancer: a retrospective study. *J Gynecol Oncol*. 2019;30(4):e57. doi:10.3802/jgo.2019.30.e57
85. Maia H, Pimentel K, Casoy J, et al. Aromatase expression in the eutopic endometrium of myomatous uteri: the influence of the menstrual cycle and oral contraceptive use. *Gynecol Endocrinol off J Int Soc Gynecol Endocrinol*. 2007;23(6):320–324. doi:10.1080/09513590701321565
86. Machado RB, de Souza IM, Beltrame A, Bernardes CR, Morimoto MS, Santana N. The levonorgestrel-releasing intrauterine system: its effect on the number of hysterectomies performed in perimenopausal women with uterine fibroids. *Gynecol Endocrinol off J Int Soc Gynecol Endocrinol*. 2013;29(5):492–495. doi:10.3109/09513590.2013.769517
87. Dominick S, Hickey M, Chin J, Su HI. Levonorgestrel intrauterine system for endometrial protection in women with breast cancer on adjuvant tamoxifen. *Cochrane Database Syst Rev*. 2015;2015(12):CD007245.
88. Napolitano A, Zanin R, Palma F, et al. Body composition and resting metabolic rate of perimenopausal women using continuous progestogen contraception. *Eur J Contracept Reprod Health Care off J Eur Soc Contracept*. 2016;21(2):168–175. doi:10.3109/13625187.2015.1079610
89. Varila E, Wahlström T, Rauramo I. A 5-year follow-up study on the use of a levonorgestrel intrauterine system in women receiving hormone replacement therapy. *Fertil Steril*. 2001;76(5):969–973. doi:10.1016/S0015-0282(01)02846-1
90. Suvanto-Luukkonen E, Kauppila A. The levonorgestrel intrauterine system in menopausal hormone replacement therapy: five-year experience. *Fertil Steril*. 1999;72(1):161–163. doi:10.1016/S0015-0282(99)00162-4
91. Depypere H, Inki P. The levonorgestrel-releasing intrauterine system for endometrial protection during estrogen replacement therapy: a clinical review. *Climacteric J Int Menopause Soc*. 2015;18(4):470–482. doi:10.3109/13697137.2014.991302
92. Bitzer J. Hormonal contraception and depression: another Pill scandal? *Eur J Contracept Reprod Health Care off J Eur Soc Contracept*. 2017;22(1):1–2. doi:10.1080/13625187.2016.1269163
93. Skovlund CW, Mørch LS, Kessing LV, Lidegaard Ø. Association of hormonal contraception with depression. *JAMA Psychiatry*. 2016;73(11):1154–1162. doi:10.1001/jamapsychiatry.2016.2387
94. Qin F, Du DF, Li XL. The effect of salpingectomy on ovarian reserve and ovarian function. *Obstet Gynecol Surv*. 2016;71(6):369–376. doi:10.1097/OGX.0000000000000323
95. North American Menopause Society. Menopause Practice: a Clinician's Guide; 2022. Available from: https://www.menopause.org/publications/professional-publications/em-menopause-practice-em-textbook. Accessed July 7, 2022.
96. Baldwin MK, Jensen JT. Contraception during the perimenopause. *Maturitas*. 2013;76(3):235–242. doi:10.1016/j.maturitas.2013.07.009
97. Inal MM, Yildirim Y, Ertopcu K, Avci ME, Ozelmas I, Tinar S. Effect of the subdermal contraceptive etonogestrel implant (Implanon) on biochemical and hormonal parameters (three years follow-up). *Eur J Contracept Reprod Health Care off J Eur Soc Contracept*. 2008;13(3):238–242. doi:10.1080/13625180802075315
98. Halmesmäki K, Hurskainen R, Tiitinen A, et al. A randomized controlled trial of hysterectomy or levonorgestrel-releasing intrauterine system in the treatment of menorrhagia-effect on FSH levels and menopausal symptoms. *Hum Reprod Oxf Engl*. 2004;19(2):378–382. doi:10.1093/humrep/deh055
99. Juliato CT, Fernandes A, Marchi NM, Castro S, Olivotti B, Bahamondes L. Usefulness of FSH measurements for determining menopause in long-term users of depot medroxyprogesterone acetate over 40 years of age. *Contraception*. 2007;76(4):282–286. doi:10.1016/j.contraception.2007.06.005
100. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC guidance (January 2005) contraception for women aged over 40 years. *J Fam Plann Reprod Health Care*. 2005;31(1):51–63. doi:10.1783/0000000052973086
101. Regione Emilia-Romagna. Salute.Assessorato politiche per la salute; Relazione sull'interruzione volontaria digravidanza in Emilia-Romagna nel 2020 [Health Policy Department; Report on the voluntary termination of pregnancy in Emilia-Romagna in 2020]; 2021. Available from: https://salute.regione.emilia-romagna.it/siseps/applicazioni/ig/documentazione. Accessed February 1, 2022. Italian

International Journal of Women's Health Dovepress

Publish your work in this journal

The International Journal of Women's Health is an international, peer-reviewed open-access journal publishing original research, reports, editorials, reviews and commentaries on all aspects of women's healthcare including gynecology, obstetrics, and breast cancer. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: https://www.dovepress.com/international-journal-of-womens-health-journal

Check for updates

DOI: 10.1002/ijgo.15446

SPECIAL ARTICLE

International Journal of Gynecology & Obstetrics FIGO WILEY

FIGO Preconception Checklist: Preconception care for mother and baby

Chiara Benedetto[1,2] | Fulvio Borella[1] | Hema Divakar[2] | Sarah L. O'Riordan[3,4] | Martina Mazzoli[1] | Mark Hanson[5] | Sharleen O'Reilly[3] | Bo Jacobsson[6,7,8,9] | Jeanne A. Conry[10] | Fionnuala M. McAuliffe[3,4] | FIGO Committee on Well Woman Healthcare, FIGO Committee on the Impact of Pregnancy on Long-Term Health

[1]Department of Obstetrics and Gynecology, Sant'Anna University Hospital, Torino, Italy

[2]FIGO Committee on Well Woman Health Care, London, UK

[3]UCD Perinatal Research Centre, National Maternity Hospital, University College Dublin, Dublin, Ireland

[4]FIGO Committee on the Impact of Pregnancy on Long-Term Health, London, UK

[5]Institute of Developmental Sciences, University of Southampton, Southampton, UK

[6]FIGO Division of Maternal and Newborn Health, London, UK

[7]Department of Genes and Environment, Norwegian Institute of Public Health, Oslo, Norway

[8]Department of Obstetrics and Gynecology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

[9]Department of Obstetrics and Gynecology, Sahlgrenska University Hospital, University of Gothenburg, Gothenburg, Sweden

[10]The Environmental Health Leadership Foundation, California, USA

Correspondence
Fionnuala M. McAuliffe, UCD Perinatal Research Centre, National Maternity Hospital, University College Dublin, Dublin, Ireland.
Email: fionnuala.mcauliffe@ucd.ie

Abstract

The preconception period is a unique and opportunistic time in a woman's life when she is motivated to adopt healthy behaviors that will benefit her and her child, making this time period a critical "window of opportunity" to improve short- and long-term health. Improving preconception health can ultimately improve both fetal and maternal outcomes. Promoting health before conception has several beneficial effects, including an increase in seeking antenatal care and a reduction in neonatal mortality. Preconception health is a broad concept that encompasses the management of chronic diseases, including optimal nutrition, adequate consumption of folic acid, control of body weight, adoption of healthy lifestyles, and receipt of appropriate vaccinations. Use of the FIGO Preconception Checklist, which includes the key elements of optimal preconception care, will empower women and their healthcare providers to better prepare women and their families for pregnancy.

KEYWORDS
lifecourse, nutrition, pregnancy, pregnancy planning, prepregnancy counseling, vaccines

The members of the FIGO Committee on Well Woman Health Care and the FIGO Committee on the Impact of Pregnancy on Long-Term Health, 2021–2023, are listed in Appendix.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.
© 2024 The Authors. *International Journal of Gynecology & Obstetrics* published by John Wiley & Sons Ltd on behalf of International Federation of Gynecology and Obstetrics.

1 | BACKGROUND

Maternal and fetal mortality and morbidity remain a significant global health issue and are still unacceptably high.[1-3] Every day in 2020, almost 800 women died from preventable causes related to pregnancy and childbirth, with a global maternal mortality rate of 223 per 100000 live births. Nearly 95% of all maternal deaths occurred in low- and lower-middle- income countries, and most of these deaths could have been prevented.[1]

Reducing maternal mortality is the first target of the Sustainable Development Goal on health and well-being,[4] aimed at reducing the global average maternal mortality rate to below 70 per 100000 live births by 2030.[1,4] The second target is that of ending preventable deaths of newborns and children under 5 years of age, with all countries aiming to decrease neonatal mortality rates to at least as low as 12 per 1000 live births.[4]

In this context, preconception care plays a pivotal role in prevention. Indeed, in 2013 the WHO developed a global consensus on preconception care to reduce maternal and childhood mortality and morbidity, recognizing its contribution to improving maternal–fetal outcomes, in both high- and low-income countries.[5]

Preconception care is defined as: *The provision of biomedical, behavioral, and social health interventions to women and couples before conception occurs. It aims to improve their health status and reduce behaviors and individual and environmental factors that contribute to poor maternal and child health outcomes. Its ultimate aim is to improve maternal and child health, in both the short and long term.*[6] It involves, as a first step, a comprehensive assessment of those medical, social, and lifestyle factors that may affect a woman's health during pregnancy, as well as that of her child.[6]

It has been estimated that, in the 75 high-burden Countdown Countries, which together account for more than 95% of maternal, neonatal, and child deaths, increasing the coverage and quality of several interventions, including preconception care, could avert 71% of neonatal deaths (1.9 million; range 1.6–2.1 million), 33% of stillbirths (0.82 million; range 0.60–0.93 million), and 54% of maternal deaths (0.16 million; range 0.14–0.17 million) per year by 2025.[7]

Indeed, preconception care is part and parcel of the "Well Woman Health Care" vision, aimed at preventing illness and promoting wellness for girls and women across the globe.

2 | IMPACT OF PRECONCEPTION CARE ON MATERNAL–FETAL HEALTH AND NONCOMMUNICABLE DISEASES: SHORT- AND LONG-TERM EFFECTS

The association between preconception care, defined as the receipt of specific healthcare services in the 12 months before conception, and the risk of severe maternal morbidity including maternal death, was examined among 1 514 759 women in the USA. After adjusting for multiple potential confounders, any preconception care was associated with a modestly decreased risk of severe maternal morbidity (adjusted odds ratio [aOR] 0.97; 95% CI, 0.95–1.00). However, in a subgroup analysis of women with chronic diseases, such as hypertension, diabetes, or chronic kidney disease, any preconception care was associated with a significant decrease in the odds of severe maternal morbidity (aOR, 0.84; 95% CI, 0.77–0.91).[3] Preconception disorders, such as cardiovascular or mental diseases, diabetes, obesity, anemia, and HIV infection, when aggravated by pregnancy, can also become indirect causes of maternal mortality.[8] Moreover, these disorders can affect embryonic development with long-term consequences for the next generation, perpetrating the intergenerational cycle of noncommunicable diseases (NCDs).[9] Therefore, all these disorders should be assessed, managed, and followed up as part of preconception care.[10] For example, in women with pregestational diabetes mellitus, preconception care can reduce the risk of perinatal mortality by 54% (relative risk [RR] 0.46; 95% CI, 0.30–0.73).[11]

Contraceptive care, as well as gynecologic examinations, were also associated with a decrease in severe maternal morbidity (aOR, 0.84; 95% CI, 0.75–0.95 and aOR, 0.79; 95% CI, 0.71–0.88, respectively).[3]

The preconception period is a unique and opportunistic time in a woman's life when she is motivated to adopt healthy behaviors that may potentially benefit her child, making this time period a critical "window of opportunity" to improve pregnancy outcomes. Improving preconception health can ultimately improve both fetal and maternal outcomes.[12] Promoting health before conception has been reported to have several beneficial effects, including a 39% increase in seeking antenatal care and a 17% reduction in neonatal mortality (RR 0.83; 95% CI, 0.72–0.95).[13]

Preconception health is a broad concept that encompasses the management of chronic diseases, including correct nutrition, adequate consumption of folic acid, control of body weight, healthy lifestyles, and vaccinations.[14]

However, given that approximately 50% of pregnancies around the globe are unplanned, true preconception health care requires routine access to "Well Woman Health Care", which includes the professional asking—whatever the reason for the visit—one key question: "Are you interested in conceiving this year?". If the answer is no, the woman should be offered contraception advice.

If the answer is yes, then all key factors included in the FIGO Preconception Checklist should be addressed, including nutrition and weight management, which are all part of the "Well Woman Health Care" strategy.[15] The Preconception Checklist is available in downloadable, printable format in the Supporting Information to this article (Figure FIGO Preconception Checklist).

Many women do not see a healthcare professional before pregnancy, therefore the postnatal period also offers an opportunity to advise on optimal health in preparation for a next pregnancy, should it occur, and for women's long-term health.

18793479, 0, Downloaded from https://obgyn.onlinelibrary.wiley.com/doi/10.1002/ijgo.15446 by Cochrane Mexico, Wiley Online Library on [06/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

3 | PRECONCEPTION CHECKLIST: KEY FACTORS TO BE ADDRESSED

3.1 | Pre-existing chronic medical conditions

Preconception care in women with chronic medical conditions has been associated with an increased likelihood of adopting healthy behavior, such as medication adherence, folic acid intake, and smoking cessation; quiescent disease during pregnancy; and better pregnancy outcomes including reduced congenital anomalies, obstetric complications, and rates of preterm birth and low birthweight.[10]

Therefore, preconception care is essential for potentially high-risk women during pregnancy owing to pre-existing medical conditions such as metabolic, cardiovascular, neurological, autoimmune, and/or endocrine diseases. In such cases, preconception care should focus on attaining disease quiescence during the periconception period, adjusting medications to those appropriate for pregnancy before conception, as well as verifying compliance with them. Moreover, general healthy behaviors should be promoted, including those aimed at limiting exposure to pollutants and toxic chemicals.[10,15]

3.2 | Nutrition

Maternal nutrition at conception affects placental development and function, as well as fetal genomic imprinting/programming and, consequently, the child's long-term health.[16,17]

However, a thorough review of the dietary intakes of nutrients in adolescent girls and women of reproductive age in low- and middle-income countries reported that dietary deficiencies such as low iron, vitamin A, iodine, and zinc and/or calcium, remain prevalent despite the reduction in underweight mothers.[18] In high-income countries, a typical diet that includes a high intake of red meat, refined grains/sugars, and high-fat dairy products is also lacking in several important micronutrients, such as magnesium, iodine, calcium, and vitamin D.[19]

To address these issues, FIGO developed a simple Nutrition Checklist that includes questions on specific dietary requirements, body mass index (BMI), diet quality, and micronutrients. Answering these questions raises awareness, identifies potential risks, and collects information that can inform health-promoting conversations between women and their healthcare professionals. The FIGO Nutrition Checklist is free to download at: https://www.figo.org/news/figo-nutrition-checklist. A digital version (https://survey.figo.org/c/kuxayx3e) is also available, which gives individualized feedback based on answers. This checklist has been validated for use across many healthcare settings. This allows wider access through mobile phones or other electronic devices, as mobile health technologies offer information that is well accepted by women and particularly beneficial for those who have low socioeconomic status, a young age, and/or a high BMI.[20]

Obesity

Obesity is the most common medical condition affecting women of reproductive age. Around half of all women in this age group are either overweight or obese.[21] Excessive obesity increases the risk of NCDs, including type 2 diabetes and cardiovascular disease, which contribute to over 70% of global deaths annually.[22]

Moreover, obese women are at risk of vitamin D deficiency due to the vitamin sequestration in adipose tissue.[15] Obesity is an independent risk factor in pregnancy, with a higher chance of having pregnancy-associated hypertension, insulin-dependent gestational diabetes, and infants with macrosomia. Excessive gestational weight gain and postpartum weight retention may play a significant role in long-term obesity. Having one child doubles the 5- and 10-year obesity incidence for women, with many women who gain excessive weight during pregnancy remaining obese permanently.[23] Therefore, excessive gestational weight gain and/or postpartum weight retention should be considered as they significantly contribute to short- and long-term adverse health outcomes for mother, baby, and future pregnancies.[24] Women with a BMI of more than 30 should be referred to a dietician.

Underweight

Low maternal weight and BMI at conception or delivery, as well as poor weight gain during pregnancy, are associated with low birthweight, prematurity, and maternal delivery complications.[25–28]

Micronutrient deficiencies, such as low folate, iron, and/or vitamin B12, may lead to anemia and its associated adverse pregnancy outcomes.[27] It is recommended that all women are screened for anemia in the preconception period.[15] Women with severe underweight should be referred to a dietician.

3.3 | Supplementation

Folic acid

Early use of folic acid prevents neural tube defects (NTDs). Adequate levels of folate in pregnancy, measured as a red blood cell folate concentration above 906 nmol/L, can be difficult to achieve through diet alone, therefore women of reproductive age should be prescribed folic acid both during the preconception period and throughout pregnancy. NTDs occur due to the neural tube failing to close at approximately 3–4 weeks of gestation and may lead to infant mortality or long-term disability.[29] Although the proportion of NTDs that can be prevented by sufficient folate intake has not yet been established, the general consensus is that it is probably about 50%–60%.[30] Randomized controlled trials have reported significant reductions in the prevalence rates of NTDs with adequate folic acid supplementation.[31] Indeed, in low-resource countries, the introduction of periconceptional folic acid supplementation has been

18793479, 0, Downloaded from https://obgyn.onlinelibrary.wiley.com/doi/10.1002/ijgo.15446 by Cochrane Mexico, Wiley Online Library on [06/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

demonstrated to reduce the incidence of NTDs (RR 0.53; 95% CI, 0.41–0.77; two studies, $n=248\,056$), whilst iron–folic acid supplementation reduced the rates of anemia (RR 0.66; 95% CI, 0.53–0.81; six studies; $n=3430$), particularly when supplemented weekly and in a school setting.[32]

Moreover, a study of over 1.5 million women demonstrated that folic acid supplementation, taken 3 months before pregnancy, was associated with a significantly lower risk of low birthweight, miscarriage, stillbirth, and neonatal mortality, compared with no use.[33]

WHO recommends routine daily folic acid dosing for low-risk women at a dose of 0.4 mg per day, starting 3 months before conception.[34] Those at increased risk of NTDs, including women with a BMI of more than 30, a history of an NTD in a previous child, epilepsy or anticonvulsant use, and/or pre-existing type 2 diabetes, require a higher folic acid dose of 4–5 mg per day.[35]

Other micronutrients

A significant number of women of reproductive age, especially the youngest, do not meet even the minimum recommended levels of certain nutrients in their diet (known as the reference nutrient intake), in particular mineral intake. For instance, 77% of women aged 18–25 years were found to have insufficient daily dietary intakes of iodine and 96% of women of reproductive age had daily intakes of iron and folate below the recommended levels for pregnancy.[19]

Preconception supplementation of certain micronutrients is associated with a reduction in several adverse obstetric outcomes, for example calcium and vitamin D supplementation reduce the risk of pre-eclampsia[36]; myoinositol, probiotics, and micronutrient supplementation decrease the risk of preterm births (aRR 0.43; 95% CI, 0.22–0.82).[37] Moreover, preconceptional micronutrient supplementation may influence intellectual development in offspring. In fact, preconception supplementation with multiple micronutrients has been found to improve certain domains of intellectual functioning in offspring at 6–7 years of age, compared with folic acid alone.[38] Therefore, it is crucial to provide information about micronutrient supplementation during preconception counseling.

3.4 | Lifestyle variables

Tobacco smoking cessation

Tobacco use during pregnancy is associated with adverse pregnancy outcomes, including miscarriage, ectopic pregnancy, preterm delivery, fetal growth restriction, small-for-gestational-age, low birthweight, placental abruption, stillbirth, and neonatal death.[39–42] Indeed, smoking during pregnancy may cause impaired placental development, leading to a hypoxic environment with reduced provision of oxygen and micronutrients to the fetus.[41]

Stopping smoking is associated with improved pregnancy and child health outcomes, including reductions in the incidence of low birthweight, preterm birth, intensive care unit admissions, and perinatal mortality.[43]

Therefore, as cigarette smoking is one of the most important modifiable risk factors associated with adverse perinatal outcomes, smoking cessation advice should be given to women before pregnancy.

Alcohol consumption

Alcohol use during pregnancy is a leading preventable cause of birth defects and developmental disabilities, with fetal alcohol syndrome (FAS) being one of the most severe outcomes. Other adverse health effects associated with alcohol use in pregnancy include miscarriage, preterm labor, intrauterine growth restriction, and stillbirth, which all add morbidity to any potential underlying disability.[44,45] Moreover, consuming alcohol during pregnancy may lead to neuropsychological adverse outcomes in the newborn.[44,45] Regardless, alcohol use in pregnancy remains common, with a global prevalence of approximately 10%, with rates of use varying depending on the country where the woman resides.[46] In fact, the global prevalence of FAS in children and youths in the general population has been estimated to be 7.7 per 1000 population.[47]

Women should be advised to avoid drinking alcohol if they are planning a pregnancy. Currently, literature reports no recommended safe level of alcohol consumption during pregnancy. Therefore, preconception counseling should include addressing this issue prior to pregnancy.

Substance use

Women are at the greatest risk of developing a substance use disorder in their reproductive years, with the highest prevalence rates observed in adolescence and early adulthood.[48] The use of illicit drugs in pregnancy is associated with adverse maternal, fetal, and child outcomes, including abortion, neonatal abstinence syndrome, placental abruption, intrauterine growth restriction, preterm birth, hemorrhage, as well as fetal and infant mortality. Therefore, women should be advised to discontinue the use of such substances and informed about both short- and long-term risks for themselves and their babies.[49]

Exposure to toxic environmental chemicals

Links between prenatal exposure to environmental chemicals and adverse health outcomes throughout the life course, including negative impacts on fertility, pregnancy, neurodevelopment, and cancer, have been documented.[50] Some of these chemicals are still widely used, such as solvents, pesticides, phthalates, lead, methyl mercury,

18793479, 0, Downloaded from https://obgyn.onlinelibrary.wiley.com/doi/10.1002/ijgo.15446 by Cochrane Mexico, Wiley Online Library on [06/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

polycyclic aromatic hydrocarbons, bisphenol A, and per- and polyfluorinated substances. They can be found in households and workplaces, in food, water, air, and consumer products.

FIGO considers preventing exposure to environmental chemicals a priority. This involves giving women timely information on how to avoid or reduce such exposure.[50] Furthermore, the health impacts of toxic environmental chemicals can be exacerbated by climate change.[51,52] Therefore, some advice on protection against the negative consequences of climate change should also be provided during counseling.[53]

Physical activity

Establishing a pattern of regular physical activity prior to pregnancy is an important component of healthy pregnancy planning as it has a positive effect on the well-being of the mother and can contribute to the prevention of adverse maternal–fetal outcomes.[54] However, a pooled analysis of 358 population-based surveys with 1.9 million participants aged over 18 showed a global age-standardized prevalence of insufficient physical activity of about 32% in females. The highest prevalence (about 43%) of insufficient physical activity was observed in women from Latin America, the Caribbean, South Asia, and high-income Western countries.[55]

Prepregnancy risk factors for physical inactivity include a higher or lower than normal prepregnancy BMI, a lower maternal education level, and a history of previous live births.[56] Therefore, more thorough counseling should be offered to patients with these risk factors.

Indeed, the presence/absence of knowledge on healthy behaviors have been shown to be the most commonly assessed enabler/barrier to women's lifestyle behavior change during the preconception period.[57]

The FIGO Pregnancy and Noncommunicable Diseases Committee and the FIGO Committee for Reproductive Medicine, Endocrinology, and Infertility, as well as the American Society for Reproductive Medicine and the American College of Obstetricians and Gynecologists (ACOG), recommend moderate physical activity of at least 30 min a day, 5 days a week, for a minimum of 150 min of moderate exercise per week. These levels of exercise are recommended prepregnancy, during pregnancy, and postpartum,[15,58] as several studies report that pregnant women generally do not engage in much physical activity.[54] Association with dietary modifications is related to a greater weight loss than exercise alone.[15,58]

Particular attention must be paid to some categories, such as professional female athletes. To date, there is a paucity of evidence as to the effects of their physical activity during pregnancy. A recent systematic review suggests that there are no known significant negative consequences of physical activity for pregnant athletes. This would imply that pregnant women who engage in higher impact activities, including elite and competitive athletes, can approach sports with confidence.[59] On the other hand, ACOG suggests caution, stating that women performing high levels of physical activity may be at risk of hyperthermia, dehydration, and excessive weight loss.[58] These risks need to be discussed with female athletes seeking to become pregnant.

3.5 | Vaccines

A pregnant woman and her fetus/newborn are vulnerable to severe infectious diseases. Therefore, determining the immunization status of every woman in her reproductive years is of pivotal importance, whatever the reason for her consulting a healthcare professional. This would make it possible for women to be protected when and if the time comes for a pregnancy.

Vaccination to prevent maternal and perinatal adverse outcomes should be offered against hepatitis B virus, human papilloma virus, influenza, measles–mumps–rubella (MMR), meningococcal (ACWY and B), varicella, tetanus, diphtheria, and pertussis.[60,61]

As there is a theoretical risk to the fetus when the mother is given a live virus vaccine, women should be counseled to avoid becoming pregnant for 28 days after having MMR and/or varicella vaccines. Moreover, women who may get pregnant during the influenza season should be given inactivated or recombinant influenza vaccines.

3.6 | Pregnancy intervals

Short interpregnancy intervals (<6 months) are associated with preterm birth, very preterm birth, low birthweight, small-for-gestational-age, offspring death, neonatal intensive care unit admission, and congenital abnormalities.[62] Interpregnancy intervals between 6 and 12 months are also associated with increased rates of preterm birth.[63] Moreover, the length of the interpregnancy interval is a significant contributor to neonatal morbidity, whatever the gestational age at birth. Indeed, both short (<12 months) and long (>24 months) interpregnancy intervals are independently associated with a higher rate and risk of neonatal morbidity, despite preterm influences, as compared with intervals of between 12 and 24 months.[64]

These data suggest that a time lapse of between 12 and 24 months between pregnancies is most likely the optimal interval to minimize perinatal adverse outcomes[63] as well as long-term risks for maternal health, including all-cause mortality.[65] Furthermore, a woman's individual characteristics and outcome of any previous birth should also be taken into consideration when counseling on the most adequate interpregnancy interval and appropriate contraception,[66] aiming at decreasing the risks for both mothers and babies.

4 | FIGO POSITION ON PRECONCEPTION CARE

Preconception care is pivotal in improving women's health before conception to prevent short- and long-term adverse outcomes for both mothers and babies.

18793479, 0, Downloaded from https://obgyn.onlinelibrary.wiley.com/doi/10.1002/ijgo.15446 by Cochrane Mexico, Wiley Online Library on [06/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Indeed, preconception care addresses risk factors and health issues that contribute to maternal and perinatal mortality and morbidity, including pre-existing chronic medical conditions, harmful environmental exposures, infectious diseases, incorrect nutrition, unhealthy lifestyles, and inadequate interpregnancy intervals.

Therefore, it is of utmost importance for public health services to effectively and appropriately address all preconception health needs. To this aim, preconception care should be provided to all women of childbearing age by healthcare professionals during routine visits, whatever their pregnancy intentions.

FIGO's Preconception Checklist (Figure FIGO Preconception Checklist) aims to promote adequate and homogeneous preconception care in all countries worldwide.

4.1 | FIGO commitments

FIGO commits itself to advocating for the importance of preconception care and promoting initiatives for its appropriate implementation across all member societies.

FIGO will do so by:

- Disseminating and developing resources for healthcare professionals on preconception care, such as the FIGO Preconception Checklist.
- Influencing all healthcare systems, policymakers, and providers to ensure that they are made aware of the impact that preconception care has on the short- and long-term health of their populations.
- Advocating for supportive capacity-building for gynecologists, obstetricians, frontline healthcare providers, and childbirth educators.
- Providing resources to support data collection and monitoring mechanisms at institutional and country levels to assess and monitor existing preconception care practices.

AUTHOR CONTRIBUTIONS

All authors contributed to the design, planning and manuscript writing, and agree to be accountable for all aspects of the manuscript.

ACKNOWLEDGMENTS

Open access funding provided by IReL.

CONFLICT OF INTEREST STATEMENT

Mark Hanson is volunteer co-Chair of the Knowledge and Evidence Working Group, Partnership for Maternal, Newborn and Child Health. Sharleen O'Reilly has received grants from European Commission Horizon 2020, National Health and Medical Research Council of Australia, Health Research Board Ireland, Al Qasimi Foundation and University of Sharjah Grant, UCD STEM Challenge Fund, Danish Diabetes and Endocrinology Academy. Jeanne A. Conry is immediate Past President of FIGO. Fionnuala M. McAuliffe holds fiduciary or leadership roles in FIGO (Council) and EBCOG (Council). All other authors have no conflicts of interest to report.

DATA AVAILABILITY STATEMENT

Data available upon request.

REFERENCES

1. World Health Organization. Maternal mortality [website]. February 22, 2023. Accessed February 3, 2024 https://www.who.int/news-room/fact-sheets/detail/maternal-mortality
2. Geller SE, Koch AR, Garland CE, MacDonald EJ, Storey F, Lawton B. A global view of severe maternal morbidity: moving beyond maternal mortality. *Reprod Health*. 2018;15(suppl 1):98.
3. Dude AM, Schueler K, Schumm LP, Murugesan M, Stulberg DB. Preconception care and severe maternal morbidity in the United States. *Am J Obstet Gynecol MFM*. 2022;4:100549.
4. United Nations. Sustainable development goal 3 [website]. https://unric.org/en/sdg-3/. Accessed July 23, 2023
5. World Health Organization. Preconception care. Report of a regional expert group consultation 6–8 August 2013, New Delhi, India.
6. World Health Organization. *Meeting to Develop a Global Consensus on Preconception Care to Reduce Maternal and Childhood Mortality and Morbidity*. WHO; 2013.
7. Bhutta ZA, Das JK, Bahl R, et al. Can available interventions end preventable deaths in mothers, newborn babies, and stillbirths, and at what cost? *Lancet*. 2014;384:347-370.
8. Storm F, Agampodi S, Eddleston M, Sørensen JB, Konradsen F, Rheinländer T. Indirect causes of maternal death. *Lancet Glob Health*. 2014;2:e566.
9. Fleming TP, Watkins AJ, Velazquez MA, et al. Origins of lifetime health around the time of conception: causes and consequences. *Lancet*. 2018;391:1842-1852.
10. Nana M, Stannard MT, Nelson-Piercy C, Williamson C. The impact of preconception counselling on maternal and fetal outcomes in women with chronic medical conditions: a systematic review. *Eur J Intern Med*. 2023;108:52-59.
11. Wahabi HA, Fayed A, Esmaeil S, et al. Systematic review and meta-analysis of the effectiveness of pre-pregnancy care for women with diabetes for improving maternal and perinatal outcomes. *PLoS One*. 2020;15:e0237571.
12. Moos MK, Dunlop AL, Jack BW, et al. Healthier women, healthier reproductive outcomes: recommendations for the routine care of all women of reproductive age. *Am J Obstet Gynecol*. 2008;199(suppl 2):S280-S289.
13. Dean SV, Lassi ZS, Imam AM, Bhutta ZA. Preconception care: closing the gap in the continuum of care to accelerate improvements in maternal, newborn and child health. *Reprod Health*. 2014;11(Suppl 3):S1.
14. Xaverius PK, Tenkku LE, Salas J. Differences between women at higher and lower risk for an unintended pregnancy. *Womens Health Issues*. 2009;19:306-312.
15. Jacob CM, Killeen SL, McAuliffe FM, et al. Prevention of noncommunicable diseases by interventions in the preconception period: a FIGO position paper for action by healthcare practitioners. *Int J Gynecol Obstet*. 2020;151:6-15.
16. King JC. A summary of pathways or mechanisms linking preconception maternal nutrition with birth outcomes. *J Nutr*. 2016;146:1437S-1444S.
17. Montagnoli C, Santoro CB, Buzzi T, Bortolus R. Maternal periconceptional nutrition matters. A scoping review of the current literature. *J Matern Fetal Neonatal Med*. 2022;35:8123-8140.
18. Caulfield LE, VElliot V, Program in Human Nutrition, the Johns Hopkins Bloomberg School of Public Health, for SPRING. *Nutrition of Adolescent Girls and Women of Reproductive Age in Low- and Middle-Income Countries: Current Context and Scientific Basis for Moving Forward*. Strengthening Partnerships, Results, and Innovations in Nutrition Globally (SPRING) Project; 2015.

18793479, 0, Downloaded from https://obgyn.onlinelibrary.wiley.com/doi/10.1002/ijgo.15446 by Cochrane Mexico, Wiley Online Library on [06/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

19. Stephenson J, Heslehurst N, Hall J, et al. Before the beginning: nutrition and lifestyle in the preconception period and its importance for future health. *Lancet*. 2018;391:1830-1841.
20. Killeen SL, Donnellan N, O'Reilly SL, et al. Using FIGO nutrition checklist counselling in pregnancy: a review to support healthcare professionals. *Int J Gynecol Obstet*. 2023;160(suppl 1):10-21.
21. American College of Obstetricians and Gynecologists. Obesity in pregnancy: ACOG practice bulletin, number 230. *Obstet Gynecol*. 2021;137:e128-e144.
22. McAuliffe FM, Killeen SL, Jacob CM, et al. Management of prepregnancy, pregnancy, and postpartum obesity from the FIGO pregnancy and non-communicable diseases committee: a FIGO (International Federation of Gynecology and Obstetrics) guideline. *Int J Gynecol Obstet*. 2020;151:16-36.
23. Davis E, Olson C. Obesity in pregnancy. *Prim Care*. 2009;36:341-356.
24. Reed J, Case S, Rijhsinghani A. Maternal obesity: perinatal implications. *SAGE Open Med*. 2023;11:20503121231176128.
25. Ehrenberg HM, Dierker L, Milluzzi C, Mercer BM. Low maternal weight, failure to thrive in pregnancy, and adverse pregnancy outcomes. *Am J Obstet Gynecol*. 2003;189:1726-1730.
26. Dean SV, Lassi ZS, Imam AM, Bhutta ZA. Preconception care: nutritional risks and interventions. *Reprod Health*. 2014;11(Suppl 3):S3.
27. Hanson MA, Bardsley A, De-Regil LM, et al. The International Federation of Gynecology and Obstetrics (FIGO) recommendations on adolescent, preconception, and maternal nutrition: "Think Nutrition First". *Int J Gynecol Obstet*. 2015;131(suppl 4):S213-S253.
28. Nagao T, Fukui S, Ohde S, Yamanaka M. The perinatal outcomes by gestational weight gain range at 30 weeks of gestation among pre-pregnancy underweight women. *J Obstet Gynaecol Res*. 2023;49:635-640.
29. Flores AL, Vellozzi C, Valencia D, Sniezek J. Global burden of neural tube defects, risk factors, and prevention. *Indian J Community Health*. 2014;26(suppl 1):3-5.
30. Pitkin RM. Folate and neural tube defects. *Am J Clin Nutr*. 2007;85:285S-288S.
31. Crider KS, Qi YP, Yeung LF, et al. Folic acid and the prevention of birth defects: 30 years of opportunity and controversies. *Annu Rev Nutr*. 2022;42:423-452.
32. Lassi ZS, Kedzior SG, Tariq W, Jadoon Y, Das JK, Bhutta ZA. Effects of preconception care and periconception interventions on maternal nutritional status and birth outcomes in low- and middle-income countries: a systematic review. *Nutrients*. 2020;12:606.
33. He Y, Pan A, Hu FB, Ma X. Folic acid supplementation, birth defects, and adverse pregnancy outcomes in Chinese women: a population-based mega-cohort study. *Lancet*. 2016;388:S91.
34. World Health Organization. *Guideline: Daily Iron and Folic Acid Supplementation in Pregnant Women*. WHO; 2012.
35. Dwyer ER, Filion KB, MacFarlane AJ, Platt RW, Mehrabadi A. Who should consume high-dose folic acid supplements before and during early pregnancy for the prevention of neural tube defects? *BMJ*. 2022;377:e067728.
36. Gunabalasingam S, De Almeida Lima Slizys D, Quotah O, et al. Micronutrient supplementation interventions in preconception and pregnant women at increased risk of developing pre-eclampsia: a systematic review and meta-analysis. *Eur J Clin Nutr*. 2023;77:710-730.
37. Godfrey KM, Barton SJ, El-Heis S, et al. Myo-inositol, probiotics, and micronutrient supplementation from preconception for glycemia in pregnancy: NiPPeR international multicenter double-blind randomized controlled trial. *Diabetes Care*. 2021;44:1091-1099.
38. Nguyen PH, Young MF, Tran LM, et al. Preconception micronutrient supplementation positively affects child intellectual functioning at 6 y of age: a randomized controlled trial in Vietnam. *Am J Clin Nutr*. 2021;113:1199-1208.
39. Andres RL. Perinatal complications associated with maternal smoking. *Semin Neonatol*. 2005;5:231-241.
40. Pintican D, Poienar AA, Strilciuc S, Mihu D. Effects of maternal smoking on human placental vascularization: a systematic review. *Taiwan J Obstet Gynecol*. 2019;58:454-459.
41. Diamanti A, Papadakis S, Schoretsaniti S, et al. Smoking cessation in pregnancy: an update for maternity care practitioners. *Tob Induc Dis*. 2019;17:57.
42. Avşar TS, McLeod H, Jackson L. Health outcomes of smoking during pregnancy and the postpartum period: an umbrella review. *BMC Pregnancy Childbirth*. 2021;21:254.
43. Chamberlain C, O'Mara-Eves A, Porter J, et al. Psychosocial interventions for supporting women to stop smoking in pregnancy. *Cochrane Database Syst Rev*. 2017;2:CD001055.
44. Henderson J, Gray R, Brocklehurst P. Systematic review of effects of low-moderate prenatal alcohol exposure on pregnancy outcome. *BJOG*. 2007;1114:243-252.
45. Muggli E, Matthews H, Penington A, et al. Association between prenatal alcohol exposure and craniofacial shape of children at 12 months of age. *JAMA Pediatr*. 2017;171:771-780.
46. Popova S, Lange S, Probst C, Gmel G, Rehm J. Estimation of national, regional, and global prevalence of alcohol use during pregnancy and fetal alcohol syndrome: a systematic review and meta-analysis. *Lancet Glob Health*. 2017;5:e290-e299.
47. Lange S, Probst C, Gmel G, Rehm J, Burd L, Popova S. Global prevalence of fetal alcohol spectrum disorder among children and youth: a systematic review and meta-analysis. *JAMA Pediatr*. 2017;171:948-956.
48. Merikangas KR, McClair VL. Epidemiology of substance use disorders. *Hum Genet*. 2012;131:779-789.
49. Smid MC, Terplan M. What obstetrician-gynecologists should know about substance use disorders in the perinatal period. *Obstet Gynecol*. 2022;139:317-337.
50. Di Renzo GC, Conry JA, Blake J, et al. International Federation of Gynecology and Obstetrics opinion on reproductive health impacts of exposure to toxic environmental chemicals. *Int J Gynecol Obstet*. 2015;131:219-225.
51. Giudice LC, Llamas-Clark EF, DeNicola N, et al. Climate change, women's health, and the role of obstetricians and gynecologists in leadership. *Int J Gynecol Obstet*. 2021;155:345-356.
52. Corbett GA, Lee S, Woodruff TJ, et al. Nutritional interventions to ameliorate the effect of endocrine disruptors on human reproductive health: a semi-structured review from FIGO. *Int J Gynaecol Obstet*. 2022;157(3):489-501.
53. WSPEHSU. Guidance from the Western States Pediatric Environmental Health Specialty Unit, Climate Change and Pregnancy. Factsheet. 2022.
54. Chan CWH, Au Yeung E, Law BMH. Effectiveness of physical activity interventions on pregnancy-related outcomes among pregnant women: a systematic review. *Int J Environ Res Public Health*. 2019;16:1840.
55. Guthold R, Stevens GA, Riley LM, Bull FC. Worldwide trends in insufficient physical activity from 2001 to 2016: a pooled analysis of 358 population-based surveys with 19 million participants. *Lancet Glob Health*. 2018;6:e1077-e1086.
56. Donahue SM, Zimmerman FJ, Starr JR, Holt VL. Correlates of prepregnancy physical inactivity: results from the pregnancy risk assessment monitoring system. *Matern Child Health J*. 2010;14:235-244.
57. Kandel P, Lim S, Pirotta S, Skouteris H, Moran LJ, Hill B. Enablers and barriers to women's lifestyle behavior change during the preconception period: a systematic review. *Obes Rev*. 2021;22:e13235.
58. American Society for Reproductive Medicine; American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice. Prepregnancy counseling: Committee opinion no. 762. *Fertil Steril*. 2019;111:32-42.

18793479, 0, Downloaded from https://obgyn.onlinelibrary.wiley.com/doi/10.1002/ijgo.15446 by Cochrane Mexico, Wiley Online Library on [06/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

59. Wieloch N, Klostermann A, Kimmich N, Spörri J, Scherr J. Sport and exercise recommendations for pregnant athletes: a systematic scoping review. *BMJ Open Sport Exerc Med*. 2022;8:e001395.
60. Benedetto C, Carosso A, Corezzi M, Zotti CM, EBCOG. EBCOG position statement: Vaccination in pregnancy. *Eur J Obstet Gynecol Reprod Biol*. 2019;240:375-376.
61. Centers for Disease Control and Prevention. Vaccines before pregnancy [website]. November 9, 2021. Accessed February 7, 2024.https://www.cdc.gov/vaccines/pregnancy/vacc-before.html
62. Wang Y, Zeng C, Chen Y, et al. Short interpregnancy interval can lead to adverse pregnancy outcomes: a meta-analysis. *Front Med*. 2022;9:922053.
63. Lengyel CS, Ehrlich S, Iams JD, Muglia LJ, De Franco EA. Effect of modifiable risk factors on preterm birth: a population based-cohort. *Matern Child Health J*. 2017;21:777-785.
64. DeFranco EA, Seske LM, Greenberg JM, Muglia LJ. Influence of interpregnancy interval on neonatal morbidity. *Am J Obstet Gynecol*. 2015;212(386):e1-e9.
65. Weisband YL, Manor O, Friedlander Y, Hochner H, Paltiel O, Calderon-Margalit R. Interpregnancy and interbirth intervals and all-cause, cardiovascular-related and cancer-related maternal mortality: findings from a large population-based cohort study. *J Epidemiol Community Health*. 2020;74:957-963.
66. Mühlrad H, Björkegren E, Haraldson P, Bohm-Starke N, Kopp Kallner H, Brismar WS. Interpregnancy interval and maternal and neonatal morbidity: a nationwide cohort study. *Sci Rep*. 2022;18(12):17402.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Benedetto C, Borella F, Divakar H, et al. FIGO Preconception Checklist: Preconception care for mother and baby. *Int J Gynecol Obstet*. 2024;00:1-8. doi:10.1002/ijgo.15446

APPENDIX

Members of the FIGO Committee on Well Woman Health Care, 2021–2023: Hema Divakar (Chair), Chiara Benedetto (Vice Chair), Griselda Quijada, Chin-Long Chang, Tesfaye Hurissa, Paola Iturralde, Gelila Goba, Méabh Ní Bhuinneáin, Gulshan Ara, Christine Solbach, Suvarna Khadilkar, Nyawira Ngayu, Christian Jackisch, Ahmed Fawzy Galal, Elizabeth Pumpure, Diana Ramos.

Members of the FIGO Committee on Impact of Pregnancy on Long-Term Health, 2021–2023: Fionnuala McAuliffe (Chair), Liona Poon (Vice Chair), Graeme Smith, Virna Medina, Sumaiya Adam, Pat O'Brien, Moshe Hod, Esraa Algurjia, Lina Bergman, David McIntyre, Anil Kapur, Ronald Ma, Mary Rosser, Cynthia Maxwell, Claudio Sosa, Valerie Guinto, Titus Beyuo, Francisco Ruiloba.

18793479, 0, Downloaded from https://obgyn.onlinelibrary.wiley.com/doi/10.1002/ijgo.15446 by Cochrane Mexico, Wiley Online Library on [06/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Journal Pre-proof

UNIVERSAL ACCESS TO CONTRACEPTION: WOMEN, FAMILIES, AND COMMUNITIES BENEFIT

Laurel W. Rice, MD, Eve Espey, MD, MPH, Dee Fenner, MD, Kimberly D. Gregory, MD, Ms. Jacquelyn Askins, Charles J. Lockwood, MD, MHCM

PII: S0002-9378(19)31121-4

DOI: https://doi.org/10.1016/j.ajog.2019.09.014

Reference: YMOB 12885

To appear in: *American Journal of Obstetrics and Gynecology*

Received Date: 12 July 2019

Revised Date: 27 August 2019

Accepted Date: 12 September 2019

Please cite this article as: Rice LW, Espey E, Fenner D, Gregory KD, Jacquelyn Askins M, Lockwood CJ, UNIVERSAL ACCESS TO CONTRACEPTION: WOMEN, FAMILIES, AND COMMUNITIES BENEFIT, *American Journal of Obstetrics and Gynecology* (2019), doi: https://doi.org/10.1016/j.ajog.2019.09.014.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2019 Published by Elsevier Inc.

Journal Pre-proof

UNIVERSAL ACCESS TO CONTRACEPTION: WOMEN, FAMILIES, AND COMMUNITIES BENEFIT

Laurel W. RICE, MD[1], Eve ESPEY, MD, MPH[2], Dee FENNER, MD[3], Kimberly D. GREGORY, MD[4], Ms. Jacquelyn ASKINS[1], Charles J. LOCKWOOD, MD, MHCM[5]

[1]University of Wisconsin-Madison; Madison, WI; Department of Obstetrics and Gynecology

[2]University of New Mexico School of Medicine; Albuquerque, NM; Department of Obstetrics and Gynecology

[3]University of Michigan; Ann Arbor, MI; Department of Obstetrics and Gynecology

[4]Cedars-Sinai Medical Center; Los Angeles, CA; Department of Obstetrics and Gynecology

[5]University of South Florida; Tampa, FL

Corresponding Author:
Laurel W. Rice, MD
lwrice@wisc.edu
University of Wisconsin-Madison, School of Medicine and Public Health
McConnell Hall, 4th Floor
1010 Mound Street
Madison, WI 53715
608-417-4213

Conflicts of Interests:
There are no conflicts of interest to report.

Word count: 1914

Abstract word count: 154

Journal Pre-proof

Journal Pre-proof

CONDENSATION

This report reviews why contraception must be readily available to ALL women, improving their lives as well as that of their families and society.

Journal Pre-proof

Journal Pre-proof

ABSTRACT (WITH KEY WORDS)

Universal access to contraception benefits society: unintended pregnancies, maternal mortality, preterm birth, abortions, and obesity, would be reduced by increasing access to affordable contraception. Women should be able to choose when and whether to use contraception, what method to use and have ready access to their chosen method. State and national government should support unrestricted access to all contraceptives. As obstetrician-gynecologists, we have a critical mandate, based on principle and mission, to step up with leadership on this vital medical and public health issue, to improve the lives of women, their families, and society. The field of Obstetrics and Gynecology must provide the leadership for moving forward. The American Gynecological and Obstetrical Society (AGOS), representing academic and public policy leaders from across all disciplines of Obstetrics and Gynecology, is well-positioned to serve as a unifying organization, focused on developing a strong unified advocacy voice to fight for accessible contraception for all in the U.S.

Key Words: Contraception, Unintended Pregnancies, Maternal Mortality, Preterm Birth, Abortions, Obesity, Affordability, Access, Advocacy

Journal Pre-proof

Journal Pre-proof

INTRODUCTION:

Contraception is a fundamental component of health care that improves wellness, protects against a variety of adverse health conditions, prevents unplanned pregnancies, empowers women to reach their full potential, and has a positive impact on families, communities, and society. Contraceptive use has substantially contributed to women's societal advancement, enabling growing numbers of women to obtain college education, pursue advanced professional degrees, and join the paid workforce.[1] In recognition of the full impact of contraception, in 2011 the National Academy of Medicine (formerly the Institute of Medicine) recommended contraception as a key preventive health service, paving the way for the contraceptive mandate of the Affordable Care Act (ACA). The latter required insurance companies to cover FDA-approved contraceptives with no cost sharing.

In late 2018, the Trump administration issued two rules providing employers more flexibility to deny women insurance coverage for birth control.[2] The first provided exemption from the contraceptive coverage mandate to entities that object to such coverage based on religious beliefs. The second rule provided exemption to nonprofit organizations and small businesses that may have non-religious moral objections to such coverage. While a U.S. District judge issued a nationwide preliminary injunction against this new policy in January 2019, the case continues to make its way through the courts. The Trump administration also proposed that any organization that provides or refers patients for abortions be ineligible for Title X funding, which covers a range of other vital women's health services including sexually transmitted disease prevention, cancer screenings, and contraception; such restrictions will have dire consequences for women's health. The 9th US Circuit Court of Appeals upheld the Trump administration's interpretation of

Journal Pre-proof

the federal Title X statute, allowing the domestic gag rule to go into effect.[3] Legal challenges continue; the ultimate implementation of these rules will likely be determined by the Supreme Court.

The American Society of Gynecology and Obstetrics (AGOS) is an academic society of obstetrician-gynecologists; as multidisciplinary experts in women's health care and based on overwhelming evidence, we advocate for full unrestricted access to contraception. Our focus is on access, understanding the importance of a reproductive-justice based approach to contraception counseling and provision. Women should have free choice about whether and when to use contraceptives as well as the choice of contraception. Non-directive non-coercive counseling is key to honoring women's choices about their contraceptive method use or non-use. Access to contraception should not be restricted by the government and should be universally covered by private and public payers. Increased access to affordable contraception reduces unintended pregnancies, maternal mortality, preterm birth, abortions, and obesity and improves the health of women, families and communities.

UNINTENDED PREGNANCY:

In the U.S., approximately half of pregnancies are unintended, with about 48% of reproductive age women experiencing at least one unintended pregnancy.[4] Providing women with readily accessible and affordable contraception is the most effective way to reduce the rate of unintended pregnancy, and, pari passu, reduce the occurrence of abortion[5]. It will also improve health and economic issues facing women. Beginning in 2009, the privately-funded Colorado Family

Journal Pre-proof

Planning Initiative (CFPI) supported provider training and financing for the provision of long-acting reversible contraceptive (LARC) methods at Title X funded clinics.[6] As a consequence, by 2011 LARC use among 15- to 24-year-olds grew from 5% to 19%. Compared with expected fertility rates in 2011, observed rates were 29% lower among low-income 15- to 19-year-olds and 14% lower among low-income 20- to 24-year-olds. In participating Colorado counties, the proportion of high-risk births fell 24%, and abortion rates fell 34% and 18%, respectively, among women aged 15 to19 and 20 to 24. This case study provides compelling support for enhanced access to affordable contraception and further evidence that programs that increase LARC access among young, low□income women decrease unintended pregnancies.

MATERNAL MORTALITY:

Over the past three decades, the world has seen a steady decline in the number of women dying in childbirth. Unfortunately, the U.S., unlike other high-income countries, is a notable outlier, with maternal mortality continuing to climb.[7] We currently spend nearly 18% of our gross domestic product (GDP) on health care, which is high compared with health care spending in ten other high-income countries, including 9.6% (Australia) and 12.4% (Switzerland). IIn 2013, the U.S. ranked 60th in the world in maternal mortality.[8] Maternal mortality rates have risen steadily from 7.2 pregnancy-associated deaths per 100,000 births in 1987 to 17.3 deaths per 100,000 in 2013.[9] Some of this increase can be ascribed to improved surveillance, and in fact, accurate assessment of maternal deaths is critically important as the first step in addressing root causes.

The five leading causes of maternal mortality include cardiovascular disease, other medical conditions, infection/sepsis, hemorrhage, and cardiomyopathy.[9] Many of these conditions—

especially those related to the cardiovascular system—can be optimized during the preconception or interconception period, underscoring the need for enhanced access to affordable contraception during this period. Further data suggest that short interpregnancy intervals (<18 months) are associated with increased risk of adverse maternal outcomes; with women over 35 years of age at particularly high risk.[10] Enhanced access to, and use of, contraceptives would not only reduce the 45% of pregnancies in the U.S. that are unintended but could reduce maternal mortality by nearly 30%.[11]

PREMATURITY:

In 2018, for the fourth year in a row, U.S. preterm birth rates—already among the highest in the developed world—rose again to 10.02%.[12] The risk of spontaneous preterm birth increases four-fold among women whose interval between a prior delivery and the last menstrual period preceding their next pregnancy is ≤ 6 months.[13] A cohort study of over 112,000 women who were seen at least once by a provider within 18 months of delivery reported that for every month of contraceptive coverage, the risk of preterm birth decreased by 1.1%.[14] Furthermore, women with a short interpregnancy interval (<18 months) have an increased risk of small for gestational age infants and increased risk of fetal demise.[10] Providing contraception, including long-acting reversible contraception (LARC), in the immediate postpartum period has been shown to increase contraceptive use at six and 12 months. This maternal health-oriented intervention to lengthen interpregnancy intervals may be among our most effective strategies to stem the epidemic of preterm births and associated infant mortality and the long-term adverse health consequences that accrue to affected infants.[15]

Journal Pre-proof

Journal Pre-proof

PREVENTING ABORTIONS:

The primary determinant of the abortion rate is the unintended pregnancy rate. Unintended pregnancies frequently result from lack of access to contraception due to various impediments including financial barriers, inadequate health care access, lack of reproductive health providers, religious prohibitions, and personal factors such as fear, embarrassment, and lack of knowledge. The population-level association between access to contraception and abortion rates has been convincingly demonstrated in several studies. The Contraceptive CHOICE study simulated the no-cost sharing element of the ACA contraceptive mandate, enrolling nearly 10,000 women in St. Louis, MO. Women who enrolled obtained scripted counseling and their choice of contraceptive method at no cost. A substantial reduction in the abortion rate occurred in the CHOICE cohort compared to a similar population without the intervention of scripted counseling and no-cost contraception.[16] The contraceptive mandate has played a major role in improving access to contraception nationally, which has correlated with an associated decline in abortions.[17]

Despite strong evidence demonstrating the critical role of contraception in reducing the abortion rate, efforts have already weakened the ACA's contraceptive mandate. Another pillar of contraceptive access has been similarly compromised: Title X has ensured access to contraception for low-income women since 1970. New regulations severely undermine the program's success and run counter to the National Academy of Medicine's quality principles. Under proposed regulations, Title X providers will be restricted from offering evidence-based contraception care and reproductive health counseling. Instead of a focus on expanding access to contraception, a number of current state-level attempts to reduce abortions have focused on restricting or banning abortion access. In countries where abortion is illegal or highly restricted,

abortion rates are similar to those of countries where abortion is broadly legal, demonstrating that restricting abortion access is an ineffective strategy to reduce the abortion rate[18]. Additionally, most abortion-related deaths occur in countries where abortion is illegal or highly restricted[18]. With weakening of the contraceptive mandate and restrictions to Title X, access to contraception is shrinking at a time when expanded access is most needed to empower women, through non-coercive counseling, to make their own reproductive health decisions which may result in reduced unintended pregnancy and abortion and improve overall maternal, infant, and family health.[19]

OBESITY:

Obesity in pregnancy may have major health impacts. For women with obesity who decide on contraception use, universal access could reduce the number of pregnancies and increase inter-pregnancy intervals with a lifelong health impact. Obesity is the most common medical condition in women of reproductive age. Obesity during pregnancy has short term and long term adverse consequences for women. At term, the risk of cesarean delivery, endometritis, and wound complications is increased in obese women. Moreover, late pregnancy complications including gestational diabetes and preeclampsia, both of which are associated with long-term morbidities, are also increased in obese women.[20] Postpartum, obese women have an increased risk of venous thromboembolism and a higher risk of pulmonary embolism**,** depression, and difficulty with breast-feeding.[21]

A total of 50-60% of overweight or obese women gain more weight during pregnancy than recommended by National Academy of Medicine gestational weight guidelines leading to

postpartum weight retention. Additional weight increases future cardiometabolic risks and pre-pregnancy obesity in subsequent pregnancies. For women who wish to use contraception, avoiding unintended pregnancy reduces this incremental weight gain.[22] Short inter-pregnancy intervals are associated with increased risk of subsequent pre-pregnancy obesity and gestational diabetes.[23] Efforts to improve nutrition and physical activity during pregnancy and after delivery require not only a concerted effort on the part of the individuals, but potentially considerable fiscal resources and commitments of time. Populations at greatest risk often have the least resources and the greatest socioeconomic burden. Hence, obesity during pregnancy needs to be recognized as not only an individual problem but also as a major public health threat.[20] Access to safe, effective contraception enables obese women at risk for life-threatening co-morbidities during and after pregnancy to maximize their health prior to conception.

SUMMARY:

According to the World Health Organization, "The health of women and girls is of particular concern because in many societies they are disadvantaged by discrimination rooted in sociocultural factors."[24] In the U.S., the legalization of birth control access and introduction of federal family planning programs have had measurable impacts on women's lives. In 1999, the Centers for Disease Control and Prevention reported on family planning as one of the ten great public health achievements of the 20th century, noting that family planning altered the social and economic roles of women as well as allowing women to have desired smaller family sizes and desired increased inter-pregnancy intervals that improved outcomes for newborns and reduced maternal mortality[24].

Journal Pre-proof

Journal Pre-proof

Contraception must be available, affordable, and accessible to all who seek it. This health enhancing intervention alone would improve the lives of millions of women around the globe, including the U.S., as well as their families and society at large. High quality women's health care demands that patients' health be placed above politics. As women's health experts, we advocate for evidence-based strategies to optimize health including universal unrestricted access to contraception. The American Gynecological and Obstetrical Society (AGOS), representing academic and public policy leaders from across multiple disciplines of Obstetrics and Gynecology, is a committed member of the advocacy coalition to address this vitally important issue.

Journal Pre-proof

Journal Pre-proof

REFERENCES:

1. Bailey MJ, Reexamining the impact of family planning programs on US fertility: evidence from the War on Poverty and the early years of Title X, American Economic Journal: Applied Economics, 2012, 4(2):62–97
2. Fact Sheet: Final Rules on Religious and Moral Exemptions and Accommodation for Coverage of Certain Preventive Services Under the Affordable Care Act. HHS.gov. https://www.hhs.gov/about/news/2018/11/07/fact-sheet-final-rules-on-religious-and-moral-exemptions-and-accommodation-for-coverage-of-certain-preventive-services-under-affordable-care-act.html. Published November 7, 2018.
3. Reuters. Trump Abortion Referral 'Gag Rule' Survives Demands for Emergency Halt. *The New York Times*. July 11, 2019. https://www.nytimes.com/reuters/2019/07/11/us/politics/11reuters-usa-abortion-ruling.html. Accessed 7/12/19.
4. Finer L, Zolna M. Declines in Unintended Pregnancy in the United States, 2008–2011. *New Engl J Med*. 2016; 374(9):843-852. doi:10.1056/nejmsa1506575.
5. MMWR Surveill Summ. 2018 Nov 23; 66(25): 1–44.
Published online 2018 Nov 23. doi: 10.15585/mmwr.ss6625a1
6. Ricketts S, Klingler G, Schwalberg R. Game Change in Colorado: Widespread Use Of Long-Acting Reversible Contraceptives and Rapid Decline in Births Among Young, Low-Income Women. *Perspect Sex Reprod Health*. 2014;46(3):125-132.
7. Kassebaum N, Barber R, Bhutta Z et al. Global, regional, and national levels of maternal mortality, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet*. 2016;388(10053):1775-1812. doi:10.1016/s0140-6736(16)31470-2.

Journal Pre-proof

8. Kassebaum N, Bertozzi-Villa A, Coggeshall M et al. Global, regional, and national levels and causes of maternal mortality during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *The Lancet*. 2014;384(9947):980-1004. doi:10.1016/s0140-6736(14)60696-6.
9. Pregnancy Mortality Surveillance System. Maternal and Infant Health. CDC. Cdc.gov. https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pregnancy-mortality-surveillance-system.htm. Published 2019. Accessed June 4, 2019.
10. Schummers L, Hutcheon J, Hernandez-Diaz S et al. Association of Short Interpregnancy Interval With Pregnancy Outcomes According to Maternal Age. *JAMA Intern Med*. 2018;178(12):1661. doi:10.1001/jamainternmed.2018.4696
11. Ahmed S, Li Q, Liu L, Tsui AO. Maternal deaths averted by contraceptive use: an analysis of 172 countries. Lancet. 2012 Jul 14;380(9837):111-25. doi: 10.1016/S0140-6736(12)60478-4. Epub 2012 Jul 10. PMID: 22784531.
12. Hamilton BE, Martin JA, Osterman MJK, Rossen LM. Births: Provisional data for 2018. Vital Statistics Rapid Release; no 7. Hyattsville, MD: National Center for Health Statistics. May 2019.
13. Behrman RE, Butler AS. *Preterm Birth: Causes, Consequences, and Prevention*. Washington, D.C.: National Academies Press; 2007.
14. Rodriguez MI, Chang R, Thiel de Bocanegra H. The impact of postpartum contraception on reducing preterm birth: findings from California. *Am J Obstet Gynecol*. 2015 Nov; 213(5):703.e1-6. doi: 10.1016/j.ajog.2015.07.033. Epub 2015 Jul 26. PMID: 26220110
15. Raju TNK, Pemberton VL, Saigal S, Blaisdell CJ, Moxey-Mims M, Buist S; Adults Born Preterm Conference Speakers and Discussants. Long-Term Healthcare Outcomes of

Journal Pre-proof

Preterm Birth: An Executive Summary of a Conference Sponsored by the National Institutes of Health. J Pediatr. 2017 Feb;181:309-318.e1. doi: 10.1016/j.jpeds.2016.10.015. Epub 2016 Oct 31.PMID: 27806833.

16. Peipert JF, Madden T, Allsworth JE, et al. Preventing unintended pregnancies by providing no-cost contraception. *Obstet Gynecol* 2012;120:1291–7.

17. Mulligan, K. Contraception Use, Abortions, and Births: The Effect of Insurance Mandates; *Demography*. 2015 Aug; 52(4): 1195-1217; 2015.

18. Singh S, Remez L, Sedgh Gilda, et al. Abortion Worldwide 2017: Uneven Progress and Unequal Access, New York: Guttmacher Institute. https://www.guttmacher.org/report/abortion-worldwide-2017. Accessed August 22, 2019.

19. Gavin L, Moskosky S, Carter M, et al. Providing quality family planning services: Recommendations of CDC and the US Office of Population Affairs, MMWR 2014;64(4)1-54. (https://www.cdc.gov/mmwr/pdf/rr/rr6304.pdf) Accessed June 20, 2019.

20. Catalano PM, Shankar K. Obesity and pregnancy: mechanisms of short term and long term adverse consequences for mother and child, *BMJ*. 2017 Feb 8; 356:j1.

21. Duhl AJ, Paidas MJ, Ural SH, et al. Pregnancy and Thrombosis Working Group. Antithrombotic therapy and pregnancy: consensus report and recommendations for prevention and treatment of venous thromboembolism and adverse pregnancy outcomes. *Am J Obstet Gynecol* 2007; 197:457.e1-21.

22. Rasmussen KM, Yaktine AL. *Weight gain during pregnancy: reexamining the guidelines*. Washington, D.C.: National Academies Press; 2009.

23. Hutcheon JA, Nelson HD, Moskosky S et al. Short interpregnancy intervals and adverse maternal outcomes in high-resource settings: An updated systematic review. *Paedatr Perinat Epidemiol*. 2019 Jan; 33(1):O48-O59.

24. Women's health. World Health Organization. https://www.who.int/topics/womens_health/en/. Published 2019. Accessed July 5, 2019. Accessed June 10, 2019.

25. Centers for Disease Control and Prevention. *Ten Great Public Health Achievements -- United States, 1900-1999*. MMWR Morb Mortal Wkly Rep. 1999 Apr 2;48(12):241-3. https://www.cdc.gov/mmwr/preview/mmwrhtml/00056796.htm. Accessed August 22, 2019.

Journal Pre-proof

OPEN

Original Research

Method of Hormonal Contraception and Protective Effects Against Ectopic Pregnancy

Helena Kopp-Kallner, PhD, Marie Linder, PhD, Carolyn E. Cesta, PhD, Silvia Segovia Chacón, RNM, MSc, Helle Kieler, PhD, and Sofie Graner, PhD

OBJECTIVE: To estimate the incidence rates for ectopic pregnancy by contraceptive method in a cohort of women using hormonal contraception in Sweden between 2005 and 2016.

METHOD: Women aged 15–49 years with a filled prescription for a hormonal contraceptive in the Swedish Prescribed Drug Register between 2005 and 2016 were included. For each woman, all exposed woman-years were allocated to treatment episodes depending on the method of contraception. Treatment time started on the day the prescription was filled and ended on the first day of the end of supply, new eligible dispensing, pregnancy-related diagnosis and its associated estimated last menstrual period, or removal procedure. *Ectopic pregnancy* was defined as having at least two records of International Classification of Diseases, Tenth Revision code O00-, including O00.0, O00.1, O00.2, O00.8, O00.9, within 30 days or one episode of O00- and one surgical procedure for ectopic pregnancy (NOMESCO Classification of Surgical Procedures code LBA, LBC, LBD, LBE, LBW). Incidence rates per 1,000 woman-years and 95% CIs were calculated for each method of contraception.

RESULTS: The study included 1,663,242 women and 1,915 events of ectopic pregnancy. The incidence rate (95% CI) for ectopic pregnancy per method of hormonal contraception was estimated: 13.5-mg levonorgestrel (LNG) hormonal intrauterine device (IUD), 2.76 (2.26–3.35) per 1,000 woman-years; 52-mg LNG hormonal IUD, 0.30 (0.28–0.33) per 1,000 woman-years; combined oral contraception, 0.20 (0.19–0.22) per 1,000 woman-years; progestogen implants, 0.31 (0.26–0.37) per 1,000 woman-years; oral medium-dose progestogen (desogestrel 75 mg), 0.24 per 1,000 woman-years, (0.21–0.27); and oral low-dose progestogen (norethisterone 0.35 mg and lynestrenol 0.5 mg), 0.81 (0.70–0.93) per 1,000 woman-years.

CONCLUSION: Hormonal contraception lowers the risk of ectopic pregnancy markedly. The incidence rate of ectopic pregnancy among women using a low-dose hormonal IUD (13.5 mg LNG) was substantially higher than that in women using other types of hormonal contraception. This study provides real-world evidence to inform best clinical practice for women-centered contraceptive counseling.

(Obstet Gynecol 2022;139:764–70)

DOI: 10.1097/AOG.0000000000004726

Ectopic pregnancy is a major cause of maternal morbidity and mortality globally, accounting for approximately 4% of the maternal mortality in the United Kingdom.[1] Ectopic pregnancy also causes significant morbidity in the form of surgical procedures, medication with methotrexate, and reduced fertility, which may result in subsequent need for assisted reproductive technology.[2–4] Approximately 2% of all pregnancies are ectopic.[5] In Sweden, where the current study took place,

From the Department of Clinical Sciences, Danderyd Hospital, Karolinska Institute, the Department of Obstetrics and Gynaecology, Danderyd Hospital, Karolinska Institutet, Clinical Epidemiology Division/Centre for Pharmacoepidemiology, Karolinska Hospital, the Department of Laboratory Medicine, Karolinska Institute, and BB Stockholm, Danderyds Hospital, Stockholm, Sweden.

Supported by the Karolinska Institute, Sweden. The funding source had no influence on or access to the results before publication of the manuscript.

Each author has confirmed compliance with the journal's requirements for authorship.

Corresponding author: Sofie Graner, PhD, Karolinska Institutet, Clinical Epidemiology Division/Centre for Pharmacoepidemiology, Karolinska Hospital, Stockholm, Sweden; email: sofie.graner@ki.se.

Financial Disclosure

Marie Linder, Carolyn E. Cesta, Silvia Segovia Chacón, and Helle Kieler are employees of the Centre for Pharmacoepidemiology, Karolinska Institutet, which receives grants from several entities (pharmaceutical companies, regulatory authorities, and contract research organizations), including Bayer, for performance of drug safety and drug utilization studies. Helena Kopp-Kallner reports personal fees outside the submitted work from Bayer for contracted work as lecturer and serving on advisory boards and institutional fees as principal investigator for trials for Bayer outside the submitted work. The other authors did not report any potential conflicts of interest.

© 2022 The Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

ISSN: 0029-7844/22

the average incidence rate of ectopic pregnancy from 2008 to 2016 was approximately 0.83 cases per 1,000 woman-years for ages 15–49 years.[6] The incidence has increased in the past decade, and contraception failure has been discussed as one plausible factor contributing to the increase.[7] In 2019, 49% of all women of reproductive age (15–49 years) worldwide were using some form of contraception.[8]

It is estimated that approximately 450 million women use hormonal or intrauterine contraception daily worldwide.[9] Hormonal contraception may be either a combination of estrogen and a progestogen (pills, patches, or vaginal rings) or progestogen only (pills, intrauterine devices [IUDs], implants, or injections). The most effective protection from experiencing an ectopic pregnancy is to use a modern contraceptive method and, thereby, reduce risk of unintended pregnancy. Long-acting reversible contraception, including hormonal IUDs, are user independent with a low risk of unintended pregnancy and, in Sweden, are often favored by young nulliparous women.[10–13] However, if pregnancy occurs, approximately 25–50% of these pregnancies are ectopic pregnancies.[14] The risk of ectopic pregnancy with use of other hormonal contraception is less studied.[13,15–17] There are studies indicating that progestogen-only hormonal contraception is associated with an increased risk of ectopic pregnancy.[16] Currently, there are three types of hormonal IUDs available on the European market (including Sweden), containing 13.5, 19.5, and 52 mg of levonorgestrel (LNG). The hormonal IUD with 13.5 mg LNG with a smaller insertion tube was introduced in Sweden in 2014. After its introduction, use of hormonal IUDs in nulliparous women increased significantly. The hormonal IUD with the lowest dose has been reported in a small study (N=1,040 women) to be associated with a higher risk of ectopic pregnancy when compared with the 52-mg LNG hormonal IUD.[18] In 2017, new text about the risk of ectopic pregnancy was included in the summary of products characteristics.

The aim of this population-based national register study was to estimate the incidence rate for ectopic pregnancy by contraceptive method in a cohort of women aged 15–49 years using hormonal contraception in Sweden between 2005 and 2016.

METHODS

Sweden has population-based national registers, which include information for all inhabitants on demographic and health indicators such as births, dispensed drugs, and hospital contacts. The population of Sweden is approximately 10 million, and the Swedish government has given consent for each individual's data to be included. All registers include the civil registration number of each resident, a unique number assigned at birth or immigration that allows linkage of individual data between registers.[19,20] We obtained linked data from three national registers: the Prescribed Drug Register, the National Patient Register, and the Medical Birth Register. The Medical Birth Register includes maternal data such as parity, the date of the last menstrual period, and pregnancy outcomes including date of birth of the neonate. The Prescribed Drug Register includes data on dispensed substances, dispensed dose, package sizes, and formulations according to the Anatomical Therapeutic Chemical (ATC) Classification System, including the date of dispensation, from July 1, 2005.[20] The National Patient Register includes all in-patient admissions and outpatients visits to the Swedish hospitals, and their associated diagnosis according to the International Classification of Diseases, Tenth Revision (ICD-10) codes.

In a Swedish setting, most women receive contraceptive counseling by midwives at booked appointments or during drop-in visits at maternity health clinics. Most contraceptive counseling and prescription is performed by midwives within the public health system and free of charge. All medication, including hormonal contraception, is free of charge for women aged 18 years or younger. For women up to 26 years of age, contraception is subsidized. Hormonal contraception requires a prescription. Removal of long-acting reversible contraceptives is performed free of charge by a midwife at patient request. Women who choose to have contraceptive counseling, prescription, insertion, or removal performed by a medical doctor pay a fee for the visit.

In Sweden, all suspected cases of ectopic pregnancy are routinely referred by any health care professional to hospital care because of the need for rapid follow-up, repeated serum human chorionic gonadotropin testing, and assessment for surgical or medical (methotrexate) treatment.

All women in Sweden registered in the Prescribed Drug Register with a filled prescription of a hormonal contraceptive (ATC code G02B or G03A), excluding spermicides (ATC code G02BB) and emergency contraceptive pills (ATC code G03AD01 or G03AD02), between July 1, 2005, and December 31, 2016, were included in the study population. Eligible dates were all dates with filled prescriptions of a unique ATC code, excluding dates with filling of two or more different contraceptives. The date of the

first filled eligible prescription during the study period was defined as the index date. Women older than age 50 years and women who had undergone a sterilization procedure before the index date were excluded from the source population. All women were followed from the index date until their 50th birthday, sterilization, death, emigration, or the administrative end of the study data linkage (December 31, 2016).

For each woman, all exposed woman-years were allocated to treatment episodes, depending on the method of contraception: hormonal IUDs containing 13.5 mg (ATC code G02BA) or 52 mg LNG (ATC code G02BA), combined hormonal contraceptives (patches ATC code G03AA13, vaginal rings ATC code G02BB0, and pills ATC codes G03AA and G03AB), etonogestrel implants (ATC code G03AC08), oral medium-dose progestogen-only (desogestrel 75 mg, ATC code G03AC09), oral low-dose progestogen-only (norethisterone 0.35 mg and lynestrenol 0.5 mg, ATC code G03AC01-02), and medroxyprogesterone acetate injections (ATC code G03AC06). Unexposed time was not included.

The length of treatment time started at dispensing date and ended on the first day of end of supply, new eligible dispensing, pregnancy related diagnosis and its associated estimated last menstrual period, or removal procedure (for IUDs or implants). Individual dispensings were summed into treatment episodes by adding the treatment time for each dispensing with a maximum gap of seven days (grace period) between stop of the current dispensing and start of next dispensing of the same contraceptive agent. Women could reenter the cohort with a new dispensing of a prescription.

Ectopic pregnancy was defined as at least two records of ectopic pregnancy (ICD-10 code O00-, including O00.0, O00.1, O00.2, O00.8, O00.9) within 30 days or one record of ectopic pregnancy and a procedure code for surgery for ectopic pregnancy (NOMESCO Classification of Surgical Procedures code LBA, LBC, LBD, LBE, LBW) during the same treatment episode. Within the 30-day window, the first fulfilled definition of ectopic pregnancy was used as the date for the outcome.

The survival curves were adjusted for the identified available confounders age (younger than 40 years, 40 years or older), diagnosis of endometriosis (ICD-10 code N80, yes or no), and previous ectopic pregnancy (defined as above, yes or no).

Baseline characteristics of the study population were expressed as numbers and proportions. The number of events (ectopic pregnancies) and woman-years for each contraceptive method and risk factor were tabulated. Incidence rates by contraceptive method and by risk factor were calculated with 95% confidence limits using Byar's method. A sensitivity analysis excluding treatment episodes with a history of ectopic pregnancy was performed.

A Cox regression model adjusted for age, history of endometriosis, previous ectopic pregnancy, and contraceptive class was fitted to time to ectopic pregnancy, assuming proportional hazards between levels within each covariate. The analytic unit was treatment episodes, allowing each woman to contribute more than once and to more than one contraceptive method. The fitted model was used for prediction (as opposed to those observed directly in the data) of survival probabilities and was presented as graphs of 1-P compared with survival time in years for each specific combination of age, history of endometriosis, and previous ectopic pregnancy covering the 13.5-mg LNG hormonal IUD and the three most common hormonal contraceptive methods (52-mg LNG hormonal IUD, combined oral contraception, and oral medium-dose progestogen-only contraception). Ethical permission for the study was granted by the regional ethical committee in Stockholm (diary number 2014/1884-31).

RESULTS

The study population included a total of 1,663,242 women who contributed a total of 6,807,293 treatment episodes, which totalled 6,960,110 woman-years. Figure 1 describes the study population flow chart. The study participants had a mean age of 27 years, and the majority (64%) were nulliparous at the inclusion in the cohort. Table 1 describes the baseline characteristics of the participants at the index date. Combined oral contraception contributed the most woman-years (40.1%) in the cohort, followed by the 52-mg LNG hormonal IUD (24.7%). Table 2 shows the total prescriptions and associated number of woman-years per contraceptive method.

There were 1,915 ectopic pregnancies during the study period resulting in an incidence rate of 0.28 per 1,000 woman-years (95% CI 0.26–0.29). Among women with a history of endometriosis, the incidence rate was 0.25 (95% CI 0.12–0.44) per 1,000 woman-years and was 6.09 (95% CI 4.88–7.50) per 1,000 woman-years for women with a history of ectopic pregnancies. No woman in the study had both a history of previous ectopic pregnancy and endometriosis at time of inclusion in the cohort.

The 13.5-mg LNG hormonal IUD was used by 2.3% of the study population, of whom 104 had an ectopic pregnancy (incidence rate 2.76 per 1,000

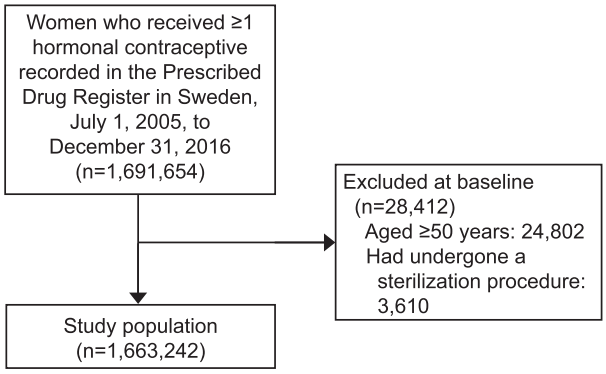

Fig. 1. Population flow chart.

Kopp-Kallner. Hormonal Contraception and Risk of Ectopic Pregnancy. Obstet Gynecol 2022.

woman-years, 95% CI 2.26–3.35). The hormonal 52-mg LNG IUD was used by 26.1% of the study population, of whom 522 had an ectopic pregnancy (incidence rate 0.30 per 1,000 woman-year, 95% CI 0.28–0.33). Table 2 and Figure 2 describe the incidence rates per method of hormonal contraception in detail. The sensitivity analysis excluding treatment episodes with a history of ectopic pregnancy (0.3%) decreased the incidence rates by 0.01–0.03 (data not shown).

The Cox regression models adjusted for history of ectopic pregnancy and endometriosis and stratified by age group are presented in Appendix 1, available online at http://links.lww.com/AOG/C638, showing the relatively higher predicted risk for ectopic pregnancy in women with a history of ectopic pregnancy independent of method of hormonal contraception. The highest predicted risk for ectopic pregnancy was seen in women younger than age 40 years with a previous history of ectopic pregnancy using the 13.5-mg LNG IUD. According to the model, approximately nine cases of ectopic pregnancy in 100 treatments are expected for the 13.5-mg LNG IUD during 2.5–3 years of use in this specific subset of the study population.

Table 1. Baseline Characteristics of Women in the Study Population at the Time of the First Contraceptive Dispensing, July 1, 2005–December 31, 2016 (N=1,663,242)

Characteristic	Value
Age (y)	27.0±9.9
Younger than 15	59,368 (3.6)
15–19	513,146 (30.9)
20–29	481,773 (29.0)
30–39	376,020 (22.6)
40–50	232,935 (14.0)
Highest level of education	
Elementary school	402,134 (24.2)
High school	544,385 (32.7)
College or university	418,262 (25.2)
Postgraduate	5,257 (0.3)
Missing	293,204 (17.6)
Parity	
0	1,059,003 (63.7)
1	15,404 (9.3)
2 or more	448,835 (27.0)
Country of birth	
Sweden	1,421,169 (85.5)
Nordic countries except Sweden	27,361 (1.7)
EU except the Nordic countries	43,223 (2.6)
Europe except EU and Nordic countries	35,340 (2.1)
Asia	86,558 (5.2)
Other	48,962 (2.9)
Missing	629 (0.0)
Medical history	
Previous ectopic pregnancy	36 (0.0)
Endometriosis	11,675 (0.7)

EU, European Union.
Data are mean±SD or n (%).

DISCUSSION

In this large, population-based prospective cohort study among women of reproductive age using hormonal contraception, the risk of ectopic pregnancy was highest among the women using 13.5-mg LNG hormonal IUDs (2.76 per 1,000 woman-years) compared with all other methods of hormonal contraception, which had similar highly protective rates. The results support the findings from a hospital-based study in which low-dose hormonal IUDs were associated with lower protective effects compared with higher-dose hormonal IUDs.[18]

The overall incidence rate of ectopic pregnancy in the study population was low, 0.28 per 1,000 woman-years from 2005 to 2016, as compared with the average approximate incidence rate of 0.83 per 1,000 woman-years for those aged 15–49 years in the Swedish population between 2008 and 2016.[6] This suggests that all the hormonal contraceptives effectively prevented pregnancies to varying degrees and subsequently lowered the absolute risk of ectopic pregnancy. The current study supports previous findings that progestogen-only methods may be associated with a lesser protective effect than combined methods.[16] This may be explained by the fact that many women continue to ovulate during use of hormonal IUDs and oral low-dose progestogen-only pills.

When adjusting the results for previous ectopic pregnancy or endometriosis, the effect of age is clearly demonstrated, with women younger than age 40 years having a higher predicted relative risk of ectopic pregnancy independent of the use of hormonal contraception. This is expected because of their

Table 2. Number of Treatment Episodes, Ectopic Pregnancies, and Woman-Years Per Hormonal Contraceptive Method, Sweden, 2005–2016

Type of Hormonal Contraception	No. of Women	No. of Treatment Episodes	Median Follow-up (y)	No. of Ectopic Pregnancies	Woman-Years	Proportion of Total Woman-Years (%)	IR/1,000 Woman-Years	95% CL
Any contraceptive	1,663,242	6,807,293	0.5	1,915	6,960,110		0.28	0.26–0.29
Hormonal IUD								
13.5 mg LNG	37,539	37,731	0.87	104	37,647	0.5	2.76	2.26–3.35
52 mg LNG	434,242	523,391	3.27	522	1,719,652	24.7	0.30	0.28–0.33
Combined hormonal contraception								
Vaginal	154,265	405,432	0.29	54	206,875	3.0	0.26	0.20–0.34
Patch	40,320	77,176	0.34	20	40,979	0.6	0.49	0.30–0.75
Oral	973,704	2,932,214	0.62	566	2,790,107	40.1	0.20	0.19–0.22
Etonogestrel implant	188,257	251,232	2.16	149	479,066	6.9	0.31	0.26–0.37
Progestogen-only contraception								
Medium-dose (oral, desogestrel 75 mg)	657,078	1,783,618	0.42	286	1,181,276	17.0	0.24	0.21–0.27
Low-dose (oral, norethisterone 0.35 mg and lynestrenol 0.5 mg)	150,597	394,696	0.46	198	245,180	3.5	0.81	0.70–0.93
Medroxyprogesterone acetate injection	91,800	401,803	0.36	16	259,327	3.7	0.06	0.04–0.10
By age (y)								
Younger than 40	1,430,307	5,752,697	0.50	1,834	5,709,869		0.32	0.31–0.34
40 or older	384,403	1,054,596	0.53	81	1,250,240		0.06	0.05–0.08
Endometriosis								
No	1,651,567	6,762,183	0.50	1,904	6,915,450		0.28	0.26–0.29
Yes	12,715	45,110	0.46	11	44,660		0.25	0.12–0.44
Previous ectopic pregnancy								
No	1,663,206	6,788,680	0.50	1,827	6,945,662		0.26	0.25–0.28
Yes	6,558	18,613	0.43	88	14,448		6.09	4.88–7.50

IR, incidence rate; CL, confidence limit; IUD, intrauterine device; LNG, levonorgestrel.

higher fertility. For all subgroups, the 13.5-mg LNG hormonal IUD was associated with the lowest protective effect, most evident for the women with a history of ectopic pregnancy, which has been reported previously.[15]

The strength of this study is its large population size, with prospectively collected data comprising all women in Sweden using hormonal contraception during the study period, assuring generalizability of the results and reduced risk of selection or recall bias. The Swedish population-based National Patient Register contains information on all inpatient and outpatient care in the Swedish hospitals, allowing information on known risk factors such as history of ectopic pregnancy or endometriosis to be included. The analyses were adjusted for women with a diagnosis of endometriosis, a common condition, but the prevalence may be underestimated when using diagnosis data from the patient register, because severe cases of endometriosis are predominantly seen in hospitals. Consequently, the effect of endometriosis on ectopic pregnancy may be overestimated. The data were not adjusted for other known risk factors of ectopic pregnancy, including history of pelvic inflammatory disease, chlamydia infection, or tubal surgery, because none of these conditions are contraindications for the use of any of the hormonal contraceptive methods, including IUD.[21,22]

The limitations of the study include the lack of information on smoking in the Swedish health registers. Smoking is a possible contraindication for combined oral contraception, especially if the woman

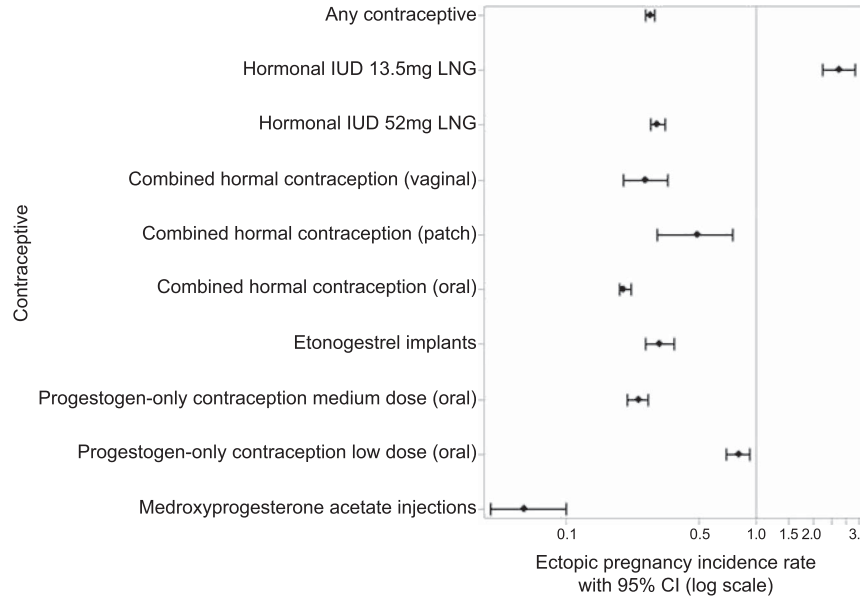

Fig. 2. Crude incidence rates and 95% CIs for ectopic pregnancies per method of hormonal contraception and covariates, Sweden 2005–2016 (log scale). Progestogen-only contraception medium-dose: desogestrel 75 mg; progestogen-only contraception low-dose: norethisterone 0.35 mg and lynestrenol 0.5 mg. IUD, intrauterine device; LNG, levonorgestrel.

Kopp-Kallner. Hormonal Contraception and Risk of Ectopic Pregnancy. Obstet Gynecol 2022.

is older than age 40 years. This may influence the results; however, we judge this effect to be minor. Other limitations include difficulties confirming the actual use of contraception. It is known that early discontinuation rates differ between methods of hormonal contraception.[23,24] In the current study it is assumed that the women are currently using the prescribed hormonal contraception if they filled a prescription valid for a certain period and have no record in the registers for indicating otherwise (such as a pregnancy related diagnosis, or removal procedure for IUD or implant). Records of filled prescriptions do not capture actual use. We therefore do not know whether or when the dispensed contraception is used but make the assumption that use, and therefore treatment time, begins on the date of dispensation. Hence, the study may underestimate the protective effect of hormonal contraception on the risk of ectopic pregnancy. Further, the Prescribed Drug Register does not include treatment without prescription (eg drugs given during inpatient care). However, because hormonal contraception is exclusively prescribed as outpatient care, the potential missed treatment episodes are assumed to be negligible in this study. The risk of missing cases of ectopic pregnancy is assumed to be small, because all cases of ectopic pregnancy in Sweden are referred to hospitals for assessment of need for surgical or medical treatment and follow-up. The 13.5-mg LNG IUD has been available on the market in Sweden since January 2014. Because our study period ended in 2016, we could not study the effects on the risk of ectopic pregnancy for the 3-year duration of its use in the majority of the users. In a previous study from our research team, the risk of ectopic pregnancy among users of the13.5-mg LNG hormonal IUD was highest in the beginning of use.[18] This may indicate a possible overestimation of the risk of ectopic pregnancy among users of the 13.5-mg LNG hormonal IUD in the current study. However, the more than fivefold relative higher incidence rate of ectopic pregnancy for the 13.5-mg LNG hormonal IUD is unlikely to be fully explained by this overestimation.

These findings are clinically relevant for providing real life evidence when providing counseling about methods of contraception to women who wish to preserve fertility. Hormonal IUDs are user-friendly and safe to use, providing women with highly effective and reversible long-acting contraception with few side effects. The results of the current study indicate that the 13.5-mg LNG hormonal IUD should not be recommended for women who are concerned about the risk of ectopic pregnancy. The 13.5-mg LNG hormonal IUD was marketed to a younger (or primiparous) population owing to its smaller size compared with the 52-mg LNG hormonal IUD. A hormonal IUD containing 19.5 mg LNG and with the same size as the 13.5-mg LNG hormonal IUD was approved for the Swedish market in November 2016. Hence, it has not been possible to study the product during the current study period. Further research is needed on the 19.5-mg LNG hormonal IUD and risk of ectopic pregnancy in real-life settings.

REFERENCES

1. Kumar V, Gupta J. Tubal ectopic pregnancy. BMJ Clin Evid 2015;2015:1406.
2. Baggio S, Garzon S, Russo A, Ianniciello CQ, Santi L, Laganà AS, et al. Fertility and reproductive outcome after tubal ectopic pregnancy: comparison among methotrexate, surgery and expectant management. Arch Gynecol Obstet 2021;303:259–68. doi: 10.1007/s00404-020-05749-2
3. Varma R, Gupta J. Tubal ectopic pregnancy. BMJ Clin Evid 2012;2012:1406.
4. Li J, Jiang K, Zhao F. Fertility outcome analysis after surgical management of tubal ectopic pregnancy: a retrospective cohort study. BMJ Open 2015;5:e007339. doi: 10.1136/bmjopen-2014-007339
5. Farquhar CM. Ectopic pregnancy. Lancet 2005;366:583–91. doi: 10.1016/s0140-6736(05)67103-6
6. National Board of Health and Welfare. Statistics database for pregnancies, births and newborns from the Swedish Medical Birth Register. Accessed March 24, 2021. https://sdb.socialstyrelsen.se/if_par/resultat.aspx
7. Rana P, Kazmi I, Singh R, Afzal M, Al-Abbasi FA, Aseeri A, et al. Ectopic pregnancy: a review. Arch Gynecol Obstet 2013; 288:747–57. doi: 10.1007/s00404-013-2929-2
8. United Nations Department of Economic and Social Affairs, Population Division. World fertility and family planning 2020: highlights. United Nations; 2020.
9. United Nations, Department of Economic and Social Affairs, Population Division. Contraceptive use by method 2019: data booklet. Accessed March 24, 2021. https://www.un.org/development/desa/pd/sites/www.un.org.development.desa.pd/files/files/documents/2020/Jan/un_2019_contraceptiveusebymethod_databooklet.pdf
10. Rosenstock JR, Peipert JF, Madden T, Zhao Q, Secura GM. Continuation of reversible contraception in teenagers and young women. Obstet Gynecol 2012;120:1298–305. doi: 10.1097/aog.0b013e31827499bd
11. Heinemann K, Reed S, Moehner S, Minh TD. Comparative contraceptive effectiveness of levonorgestrel-releasing and copper intrauterine devices: the European Active Surveillance Study for Intrauterine Devices. Contraception 2015;91:280–3. doi: 10.1016/j.contraception.2015.01.011
12. Winner B, Peipert JF, Zhao Q, Buckel C, Madden T, Allsworth JE, et al. Effectiveness of long-acting reversible contraception. N Engl J Med 2012;366:1998–2007. doi: 10.1056/NEJMoa1110855
13. Antell K, Deshmukh P, Brown EJ. Contraception update: intrauterine devices. FP Essent 2017;462:20–4.
14. Barnhart KT. Clinical practice. Ectopic pregnancy. N Engl J Med 2009;361:379–87. doi: 10.1056/NEJMcp0810384
15. Li C, Zhao WH, Zhu Q, Cao SJ, Ping H, Xi X, et al. Risk factors for ectopic pregnancy: a multi-center case-control study. BMC Pregnancy Childbirth 2015;15:187. doi: 10.1186/s12884-015-0613-1
16. Callahan R, Yacobson I, Halpern V, Nanda K. Ectopic pregnancy with use of progestin-only injectables and contraceptive implants: a systematic review. Contraception 2015;92:514–22. doi: 10.1016/j.contraception.2015.08.016
17. Parazzini F, Ferraroni M, Tozzi L, Benzi G, Rossi G, La Vecchia C. Past contraceptive method use and risk of ectopic pregnancy. Contraception 1995;52:93–8. doi: 10.1016/s0010-7824(95)00142-5
18. Graner S, Mc Taggart J, Nordström F, Melander E, Widenberg J, Kopp Kallner H. Levonorgestrel intrauterine contraceptive systems (13.5 mg and 52 mg) and risk of ectopic pregnancy. Acta Obstet Gynecol Scand 2019;98:937–43. doi: 10.1111/aogs.13564
19. Ludvigsson JF, Almqvist C, Bonamy AK, Ljung R, Michaëlsson K, Neovius M, et al. Registers of the Swedish total population and their use in medical research. Eur J Epidemiol 2016;31: 125–36. doi: 10.1007/s10654-016-0117-y
20. Wettermark B, Hammar N, Fored CM, Leimanis A, Otterblad Olausson P, Bergman U, et al. The new Swedish Prescribed Drug Register–opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiol Drug Saf 2007;16:726–35. doi: 10.1002/pds.1294
21. FSRH UK medical eligibility criteria for contraceptive use (UK MEC). Accessed December 1, 2021. https://www.fsrh.org/standards-and-guidance/uk-medical-eligibility-criteria-for-contraceptive-use-ukmec/
22. Long-acting reversible contraception: implants and intrauterine devices. Practice Bulletin No. 186. American College of Obstetricians and Gynecologists. Obstet Gynecol 2017;130:e251–69. doi: 10.1097/aog.0000000000002400
23. Pinter B. Continuation and compliance of contraceptive use. Eur J Contracept Reprod Health Care 2002;7:178–83.
24. Krashin J, Tang JH, Mody S, Lopez LM. Hormonal and intrauterine methods for contraception for women aged 25 years and younger. The Cochrane Database of Systematic Reviews 2015, Issue 8. Art. No.: CD009805. doi: 10.1002/14651858.CD009805.pub3

PEER REVIEW HISTORY

Received September 18, 2021. Received in revised form December 8, 2021. Accepted December 16, 2021. Peer reviews and author correspondence are available at http://links.lww.com/AOG/C639.