



SEÑOR

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

REF: Expediente 10-054-915.
Recurso de reposición contra la Resolución 35247 de 06 de junio de 2013, por la cual se concede una patente de invención.

TÍTULO: UN SISTEMA INTRAUTERINO PARA LA RETENCION DE UN COMPUESTO BIOLOGICAMENTE ACTIVO QUE COMPRENDE, UN DEPOSITO DEL COMPUESTO, UNA ESTRUCTURA QUE DEFINE UN ESPACIO INTERIOR PARA RECIBIR EL DEPOSITO Y UNO O MAS ELEMENTOS DE RETENCION.

PUBLICACIÓN: GACETA No. 627 del 20/04/2011 N° de publicación 294.

PRIORIDAD: EP 07120191.7 de 07/11/2007

SOLICITANTE: N.V. ORGANON.

APODERADO: LUZ CLEMENCIA DE PÁEZ

TRÁMITE: RECURSO DE REPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **LABORATORIO FRANCO-COLOMBIANO, LAFRANCOL S.A.**, asunto de la referencia, de manera respetuosa, y dentro de los términos de ley, presento recurso de reposición contra la Resolución 35247 de 06 de junio de 2013 por la cual se concede a la solicitud 10-054-915 el privilegio de patente de invención.

I. PETICIÓN

Sírvase, Señor Superintendente, reponer íntegramente la resolución 35247 de 06 de junio de 2013, por la cual se declaró infundada la oposición presentada y se otorgó el privilegio de patente solicitado en el expediente de la referencia, y en su reemplazo emitir otra que, con fundamento en los argumentos expuestos en el presente escrito, declare fundada dicha oposición y niegue el privilegio de patente mencionado, procediendo luego al definitivo archivo del expediente en cuestión.

II. FUNDAMENTOS DEL RECURSO Y RAZONES DE INCONFORMIDAD.

La resolución 35247 del 06 de junio de 2013 emitida por esa Superintendencia otorga patente de invención para la solicitud de la referencia; sin embargo, como se expone a continuación, la materia reclamada carece de nivel inventivo y aplicación industrial y como consecuencia de ello, el dispositivo intrauterino reclamado en la solicitud de la referencia no es susceptible de protección patentaria.

En cuanto hace al Concepto del Examinador Técnico sobre la Oposición presentada por Lafrancol S.A.:

En la Resolución 35247 se expone que las anterioridades presentadas en la Oposición no desvirtúan la materia reclamada por el solicitante, en los siguientes términos:

De acuerdo con lo expuesto, considera esta Superintendencia que los argumentos presentados por la sociedad opositora no están debidamente sustentados, ya que se hace especial énfasis en los compuestos farmacéuticos y no en el aparato que usa dichos compuestos, lo cual es objeto de reclamación en la presente solicitud, por lo mismo, no prosperan frente a la solicitud que aquí se analiza, como elementos que permitan desvirtuar su patentabilidad.

En efecto, según el examinador las anterioridades citadas en la oposición no afectan la patentabilidad de la invención por los siguientes motivos:

- a. Los documentos US3656483 y US4102998 no revelan por separado la totalidad de las características reclamadas en la solicitud.
- b. No sería obvio para una persona versada en la materia derivar lo reclamado de los documentos en mención.

Teniendo en cuenta la respuesta del Examinador y sus argumentos técnicos, nos permitimos presentar en este escrito las razones por las cuales su concepto es equivocado y los motivos por los cuales la solicitud 10-054-915 concedida mediante la Resolución 35247 no cumple con los requisitos de patentabilidad, veamos:

- El capítulo reivindicatorio carece de claridad, concisión y soporte en la descripción para todas y cada una de las modalidades de sistemas intrauterinos incluidos en el alcance de la reivindicación principal.
- Aparentemente la solicitud fue evaluada por un Examinador técnico que no podía colocarse en el nivel de un técnico medio versado en la materia reclamada: Según la materia divulgada por la presente solicitud, se observa que el problema técnico que ésta buscaba resolver era controlar la velocidad de liberación del principio activo dentro del útero (ver resumen de la solicitud); por lo tanto, para evaluar dicha propiedad del dispositivo y del polímero EVA que contiene el principio activo, era necesario tener claros conceptos tales como farmacodinamia, biodisponibilidad, liberación de fármacos, formas farmacéuticas y liberación prolongada, entre otras. Sin embargo, de acuerdo con lo consignado en el Oficio 22698 (11/12/2012) y en la Resolución 35247 (06/06/2013) el Examinador parece no tener la formación específica para comprender que el alcance de la materia reivindicada es amplio, pues cada sustancia farmacológica reivindicada tiene un comportamiento particular (Reivindicación 9); adicionalmente, no sería posible concluir que cualquiera de las modalidades de la invención tiene el mismo comportamiento o ventaja técnica, ni tampoco se proporcionaron pruebas biológicas que demostraran la ventaja del DIU de la solicitud en comento.
- La solicitud, además, comprende dos invenciones con alcances diferentes, circunstancia que no mereció al Examinador comentario alguno, a pesar de la evidente violación del principio de unidad de invención, que mencionaremos más adelante. Tal es el caso de las reivindicaciones 1 a 14 que se refieren a un DIU y la reivindicación 15 que se refiere a un método para “formar” cualquier sistema intrauterino:

15. Un método para formar un sistema intrauterino que comprende:

- formar una estructura que tiene un espacio interior y una estructura abierta;*
- proporcionar un depósito de un compuesto biológicamente activo y de un polímero EVA, en donde el depósito tiene superficie externa con una estructura que controla la velocidad; e*
- insertar el depósito dentro del espacio interior de tal manera que la parte sustancial de la superficie externa se expone a través de la estructura*

Por tanto, de la lectura de la reivindicación 15 se observa que su concesión afecta los diferentes procesos de obtención o de ensamble de dispositivos intrauterinos que contengan plásticos (polímeros EVA).

Se llama la atención de ese Despacho sobre este tema de particular relevancia, pues el Examinador técnico parece no comprender la forma como la reivindicación 15 afecta la producción de los SIU (Sistema intrauterino) en general, ya que, no se refiere únicamente al proceso de formación del aparato que según la Resolución 35247 “es el objeto de reclamación en la solicitud” sino que se refiere a **cualquier SIU** que contenga un polímero, es decir a la mayoría de SIU disponibles en el mercado.

Lo anterior permite advertir un problema en la decisión de concesión de la invención, pues siendo el aparato SIU el objeto real de la solicitud, no se entiende por qué razón el método de formar un SIU (reivindicación 15) se plantea como una reivindicación independiente del aparato objeto de la solicitud y es aceptado como una invención independiente de aquél.

- La solicitud carece de nivel inventivo y corresponde a una forma alternativa de realizar dispositivos intrauterinos para el control de la natalidad, o en su defecto la solicitud 10-054-915 reivindica sistemas intrauterinos alternativos que no revelan ninguna ventaja.

A continuación se argumentará con más detalle cada uno de estos puntos:

1. Falta de claridad, concisión y soporte en la descripción

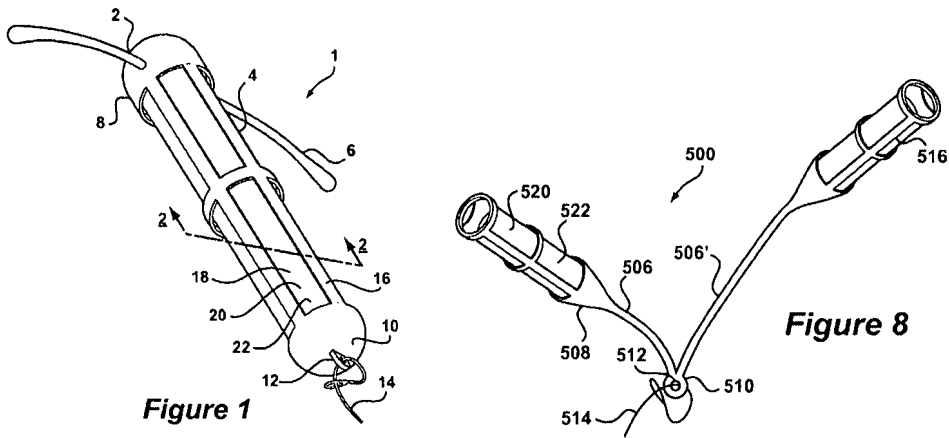
Se observa que el solicitante en la reivindicación principal caracteriza al dispositivo por la función a realizar de las partes (22), (16) y (6), por ejemplo, en el caso del polímero EVA la reivindicación menciona: “*controla una velocidad de liberación del compuesto dentro del útero y en donde el depósito tiene forma sustancialmente*

estable y no se erosiona durante el uso”, lo cual corresponde a la función del elemento.

Adicionalmente, la reivindicación principal carece de claridad y concisión pues emplea términos como “al menos 50%”, “sustancialmente”, “al menos un elemento de retención”, lo cual no permite la comprensión clara de los elementos que hacen parte de la supuesta invención:

1. Un sistema intrauterino (1) para la retención de un compuesto biológicamente activo dentro del útero de un mamífero hembra, el sistema comprende:
un depósito (22) que comprende un compuesto y un polímero EVA, en donde el polímero EVA controla una velocidad de liberación del compuesto dentro del útero y en donde el depósito tiene forma sustancialmente estable y no se erosiona durante el uso;
una estructura (16) que define un espacio interior (20) para recibir el depósito, la estructura tiene una estructura abierta que permite el acceso de al menos 50% de una superficie externa del depósito; y
al menos un elemento de retención (6) para retener la estructura dentro del útero.

Por ejemplo, la reivindicación 1 no define el número de elementos de retención (6) para retener la estructura dentro del útero, solo menciona “al menos uno”, pero esto no es conciso, pues se está extendiendo la protección de forma deliberada a cualquier dispositivo que tenga desde 1 hasta X número de elementos de retención, y por otro lado, esto parece no tener soporte en la descripción, pues allí, únicamente se presenta como modalidad un sistema intrauterino con 2 elementos de retención como se puede ver en las siguientes figuras 1 y 8:

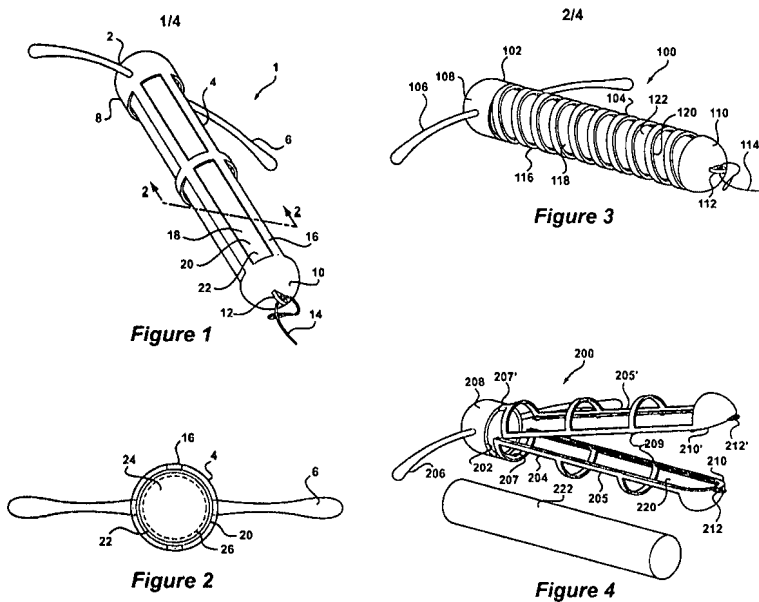


Incluso, en la descripción no se observa soporte para algo diferente a 2 elementos de retención; por lo tanto, parece ser que la reivindicación 1 tal y como fue aceptada carece de soporte en la descripción como se puede observar en el capítulo descriptivo de la solicitud original:

DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

[0035] Referring to FIG. 1, there is shown an intrauterine system 1 according to a first embodiment of the invention. The IUD 1 has a body 2 comprising a stem 4 with a pair of laterally extending arms 6 connected at its upper end 8. At a lower end 10 of the stem 4, there

En los párrafos [0035] a [0048] básicamente se describen los siguientes tipos de dispositivos que, como se puede ver, constan de dos elementos de retención:



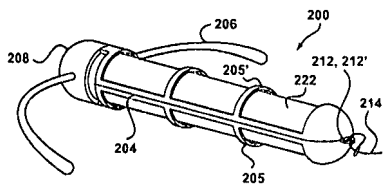


Figure 5

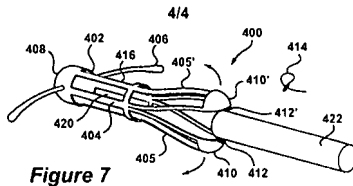


Figure 7

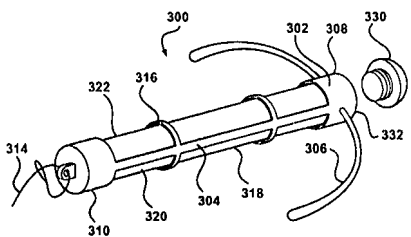


Figure 6

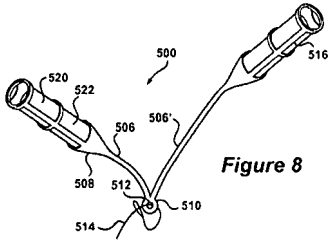


Figure 8

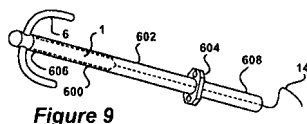


Figure 9

Por lo tanto, de la forma en que ha sido reclamado el dispositivo, el elemento para la retención (6) -revelado en la reivindicación 1-, no está debidamente sustentado ni soportado por la descripción, por lo cual se considera que la reivindicación principal no cumple con lo concebido en el artículo 30 de la Decisión 486:

“Artículo 30- Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción.

Las reivindicaciones podrán ser independientes o dependientes. Una reivindicación será independiente cuando defina la materia que se desea proteger sin referencia a otra reivindicación anterior. Una reivindicación será dependiente cuando defina la materia que se desea proteger refiriéndose a una reivindicación anterior. Una reivindicación que se refiera a dos o más reivindicaciones anteriores se considerará una reivindicación dependiente múltiple.”

Se llama la atención del Despacho sobre los argumentos mencionados hasta ahora pues el Examinador que llevó a cabo la evaluación de la solicitud no consideró la carencia de claridad y soporte de la materia reclamada en la reivindicación principal.

Por otro lado, las dimensiones del sistema intrauterino (SIU) deberían ser consideradas como parte fundamental de la materia reclamada y solo en la reivindicación 7 se menciona una dimensión de este dispositivo, de forma que la reivindicación principal no divulga las dimensiones del DIU ni la cantidad de vinil acetato (EVA) que contiene este dispositivo:

7. El sistema de acuerdo con cualquier reivindicación precedente, en donde el depósito comprende un núcleo de matriz de polímero que comprende un polímero EVA que comprende más del 10% de vinil acetato y el depósito tiene un diámetro de 1.0 mm a 3.0 mm.

En cuanto a la reivindicación 8, se observa que no divulga de forma clara y concisa el porcentaje de vinilacetato:

8. El sistema de acuerdo con cualquier reivindicación precedente, en donde el depósito comprende una membrana que rodea al depósito, preferiblemente que comprende un polímero EVA que tiene menos del 40% de vinil acetato.

Por el contenido de la materia aquí reclamada en el Concepto Técnico 22698 y en la Resolución 35247 un Examinador Químico Farmacéutico o Ingeniero Biomédico debió haber sido incluido en el análisis de patentabilidad de la solicitud, pues serían los profesionales indicados para determinar la ventaja o efecto técnico sorprendente asociado a dicho DIU.

Lo anterior se justifica por el hecho que en la solicitud existen reivindicaciones que involucran la necesidad de conocimientos FARMACOLÓGICOS para su comprensión y su estudio; tal es el caso de la reivindicación 9, en la que se reclama cualquier dispositivo que pueda tener cualquiera de los 25 compuestos esteroideos allí mencionados, y es evidente que el Examinador no se encuentra al nivel de un técnico medio versado en la materia reclamada en dicha reivindicación ya que el problema que resuelve la invención no pertenece su área técnica.

Por lo tanto, el Examinador no estaba en la posición de evaluar la carencia de soporte en la descripción de esta reivindicación y tampoco podía comprender la ventaja que puede tener este dispositivo en términos de seguridad clínica, efectos secundarios, biodisponibilidad de los activos, liberación prolongada del compuesto, efectividad en la entrega del fármaco y/o eficacia del sistema.

Se anota que la reivindicación 9 carece de claridad, concisión y soporte en la descripción, veamos:

9. El sistema de acuerdo con cualquier reivindicación precedente, en donde el compuesto es un esteroideal progestogenico seleccionado del grupo que consiste de nomegestrol acetato (NOMAc), progesterona natural, levonogestrel, etonogestrel, didrogesterona, medrogestona, acetato de medroxiprogesterona, acetato de megestrol, acetato de clormadinona, acetato de ciproterona, caproato de gestonorona, demegestona, promegestona, nesterona, trimegestona, noretisterona (noretindrona),

Por su lado, la reivindicación 10 no es clara ni concisa, pues utiliza palabras como “*al menos una superficie de depósito*”, lo que indica que puede haber más de una superficie de depósito, lo cual no se ve soportado en la descripción:

10. El sistema de acuerdo con cualquier reivindicación precedente, en donde la estructura tiene una estructura abierta que permite el acceso al menos una superficie del depósito.

2. Carencia de unidad de invención

Se reitera que la reivindicación 15 se refiere a una invención diferente a la materia reclamada de las reivindicaciones 1 a 14, pues reclama un método para formar un sistema intrauterino cualquiera.

La reivindicación 15 es independiente, y no presenta las características técnicas del SIU que supuestamente hacen parte de la invención; por lo tanto, la reivindicación 15 de forma deliberada reclama un método para producir un SIU con cualquier característica:

15. Un método para formar un sistema intrauterino que comprende:
- formar una estructura que tiene un espacio interior y una estructura abierta;

- proporcionar un depósito de un compuesto biológicamente activo y de un polímero EVA, en donde el depósito tiene superficie externa con una estructura que controla la velocidad; e
- insertar el depósito dentro del espacio interior de tal manera que la parte sustancial de la superficie externa se expone a través de la estructura.

Se considera que la concesión de esta reivindicación afecta gravemente al sector farmacéutico y de dispositivos médicos, pues se está protegiendo cualquier SIU que haya sido producido por la formación de una estructura de soporte y un depósito, como en el caso Mirena®, que consta de un sistema de liberación intrauterino:

"FORMA FARMACÉUTICA

Sistema de liberación intrauterino (SLI).

El SLI de levonorgestrel (LNG) está formado por un núcleo blanco o casi blanco, recubierto por una membrana opaca, situado sobre la parte vertical de un cuerpo en forma de T. El cuerpo en forma de T presenta un asa en uno de los extremos de la parte vertical y dos brazos horizontales en el otro extremo. Los hilos de extracción se encuentran unidos al asa. La parte vertical del SLI se introduce en el tubo de inserción, en el extremo del insertor. El SLI y el insertor se encuentran libres esencialmente de impurezas visibles."

Ficha Medicamento MIRENA Dispositivo intrauterino 20 mcg/24 h

A lo anterior, se suma el hecho que desde el año **2000** Mirena® fue aprobado por la FDA como un anticonceptivo, que actúa como un dispositivo liberador de hormona intrauterino, lo cual corresponde a la materia reclamada por el solicitante:

Mirena was approved as a contraceptive by the FDA in 2000. It is a small, flexible hormone-releasing device inserted into the uterus to prevent pregnancy. The device should be inserted by a trained health care professional.¹

Adicional a la falta de claridad de la reivindicación 15 en comentario, en lo que se refiere a las dimensiones del dispositivo, al material y a los activos que puede involucrar, la referida reivindicación no aporta ninguna ventaja que haga inventivo el método allí reclamado.

Teniendo en cuenta el artículo 52 de la D. 486, se observa, en efecto, que esta reivindicación 15 puede afectar cualquier método para obtener variados dispositivos intrauterinos, más aún cuando éste método es tan amplio y tan poco específico:

¹ <http://www.fda.gov/newsevents/newsroom/pressannouncements/2009/ucm184747.htm>

"Artículo 52.- La patente confiere a su titular el derecho de impedir a terceras personas que no tengan su consentimiento, realizar cualquiera de los siguientes actos:

a) cuando en la patente se reivindica un producto:

i) fabricar el producto;

ii) ofrecer en venta, vender o usar el producto; o importarlo para alguno de estos fines; y,

b) cuando en la patente se reivindica un procedimiento:

i) emplear el procedimiento; o

ii) ejecutar cualquiera de los actos indicados en el literal a) respecto a un producto obtenido directamente mediante el procedimiento." Negrilla fuera del texto

Como vemos, la reivindicación 15 se refiere a una invención diferente que la mencionada en las reivindicaciones 1 a 14, y además, carece de claridad, concisión y soporte en la descripción, especialmente, en lo que hace a la ventaja que dicho método tiene sobre los mencionados en el estado del arte.

Habida cuenta de lo anterior, la concesión del privilegio patentario solicitado, haría nulo el derecho otorgado, de acuerdo con lo establecido por los artículos 25 de la Decisión 486, en consonancia con lo dispuesto por el artículo 75, literales d) y e) de la misma norma.

3. Objeciones al nivel inventivo

Sobre el particular, presentamos una aproximación sobre los Sistemas intrauterinos:

- Los métodos anticonceptivos tipo dispositivo intrauterino (DIU) tienen un potencial de prevención de embarazos y un mecanismo similar, reconocido desde hace 2.500 años (Hipócrates lo inventó). Desde 1928 se modernizan los DIU y Richard Richter aparece con un elemento de este estilo para ser colocado al interior del útero, hecho de metal y seda.
 - La evolución de los DIU ha permitido desde entonces mejorar los elementos de fabricación, pero manteniendo el mismo principio que explica su efecto
-

anticonceptivo. Han mejorado los materiales, y por ello, desde 1960 se vienen haciendo en **polietileno (plástico, polímero EVA)**, que al no tener otras sustancias, hace que a los DIU se le considere “inertes”.

- Nuevamente la evolución de este elemento, llevó a que se adicionaran otras sustancias para aumentar su potencia anticonceptiva; así fue como inicialmente se introdujeron segmentos de cobre (apareció la T de cobre en 1970), pero manteniendo la matriz de **plástico**; este cambio dio una nueva generación de DIU denominada “DIU activos”, los cuales tienen alta eficacia anticonceptiva, pero producen un alto nivel de sangrado e irregularidad menstrual.
- A partir de **1990**, la sustancia activa que se adicionó a la matriz de plástico fue el Levonorgestrel, invento de Tapani Luukkanen, con lo cual se eliminó el efecto secundario de hemorragias producido por el DIU en si mismo y se aumentó la eficacia anticonceptiva. A este dispositivo se le denominó endoceptivo y se registró con el nombre Mirena®. Este método fue patentado por Jenapharm®, laboratorio de investigación alemán, que actualmente forma parte de Bayer-Schering.
- Mirena® fue introducido al mercado colombiano en **2003**, pero nunca fue patentado en el país. Desde 2012, fue introducido en el listado de medicamentos y dispositivos médicos del POS.
- El SIU del expediente 10-054-915 **consta de una forma conocida (T)** que como se ve, se viene utilizando como matriz funcional para elementos anticonceptivos intrauterinos anteriores. Utiliza el mismo **material de base (plástico, polímero EVA)** y de la misma manera, los contenidos hormonales del mismo no son desarrollo de Organon® o de MSD®, sino sustancias conocidas que son usadas ampliamente en otros métodos hormonales (inyectables, orales o subdérmicos).
- Desde ese punto de vista, lo único realmente diferencial en la invención objeto de este recurso sería el mecanismo de liberación, lo que tampoco representa una ventaja significativa, pues los otros métodos deben demostrar la estabilidad de los niveles hormonales en las pacientes sometidas a los

estudios preliminares de biodisponibilidad, obligatorios según la legislación colombiana para cualquier nueva forma farmacéutica.

- Como es evidente, este tipo de dispositivo no ha implicado una innovación en diseño, farmacología, eficacia anticonceptiva o principios activos, por lo cual no existen argumentos para sustentar su inexistente patentabilidad.
- De lo anterior, se concluye que la forma de T del dispositivo intrauterino es la más usada y que el dispositivo siempre ha sido hecho de plástico², como el presentado por el solicitante como “polímero EVA” que corresponde a un polímero termoplástico, y que éstas son las características más comunes de estos dispositivos.

Formas farmacéutica de liberación modificada

Según el capítulo reivindicatorio de la solicitud 10-054-915 la estructura (16) tiene una especie de ventana que le permite a la superficie del depósito (22) estar en un contacto mayor con el espacio exterior en donde éste se aloja, el útero. Según el problema planteado por el solicitante, esta ventana es la que permite un control en la velocidad de liberación del principio activo, lo cual es obvio desde el punto de vista de un experto en la materia pues, a mayor superficie de contacto de la forma farmacéutica con el sitio de liberación del fármaco, mayor control de velocidad del mismo, lo que además, depende de las características fisicoquímicas de los activos y excipientes empleados:

Comprimidos matriciales hidrófilos de hinchamiento ilimitado

Son comprimidos que al entrar en contacto con agua forman rápidamente un gel en toda su superficie. Este gel establece una barrera de difusión para las moléculas del principio activo que entran en estado de disolución. A medida que el excipiente polimérico que constituye la matriz se hidrata, la gelificación avanza a una determinada velocidad hacia el núcleo sólido, donde el polímero se encuentra en estado no hidratado. Puede presentarse asimismo un mecanismo de erosión de la capa gelificada externa que también contribuye al proceso de liberación del principio activo.

Es de notar que existen muchos tipos de matrices y múltiples factores a tener en cuenta para lograr la liberación del fármaco en el sitio deseado como son, entre otros, los excipientes, el sitio en el cual se requiere la entrega del fármaco, la farmacodinamia, el tipo de liberación que se desea, la seguridad del activo asociado, la estabilidad del activo, el proceso de liberación, el tiempo en el cual se desea la liberación del fármaco y el medio en el cual se liberará el fármaco.

En el caso de formas farmacéuticas como el “depósito (22)” que está dentro del dispositivo médico “estructura (16)” para la liberación de un activo en el interior del útero por un tiempo prolongado (no especificado), la superficie de exposición al sitio de liberación es clave para “controlar” la velocidad de liberación del fármaco.

Teniendo en cuenta, que la forma farmacéutica polimérica puede sufrir ciertas transformaciones como se presenta en el recorte anterior al estar dentro del útero, es obvio que mayor será la capacidad de control sobre la velocidad de la liberación del activo al aumentar la superficie expuesta.

Por lo anterior, se considera que aumentar la superficie de exposición al “depósito (16)” en el ambiente intrauterino no brinda una ventaja técnica sorprendente y más aún cuando no se han presentado datos contundentes que demuestren el verdadero efecto “estructura (22)-depósito(16)” sobre la liberación del activo. Se observa que en efecto se trata de un DIU alternativo y según lo descrito por el solicitante, se controla la velocidad pero no se revela ni se describe si el efecto es aumentar o disminuir la velocidad de dicha liberación.

Pertinencia de los documentos presentados por la Oposición

Se observa que los documentos mencionados por la oposición US3656483 y US4102998 efectivamente revelaban “al menos un elemento de retención (6) para retener la estructura dentro del útero”, y las partes de estructura (16) y depósito (22) reclamados por el solicitante.

2 <http://es.wikipedia.org/wiki/Etilvinilacetato>

A continuación se presenta una modalidad de SIU revelada por las anterioridades y la solicitud en un cuadro comparativo, en el cual se observa que las características principales ya habían sido divulgadas por documentos del arte previo; adicionalmente, se anota que el documento **US3656483** menciona el uso de un material inerte como el plástico o el polímero EVA:

Solicitud CO 10-054-915	US3656483	US4102998
SIU	SIU de material inerte	SIU de material inerte
Depósito (22 que comprende un compuesto y un polímero EVA)	Deposito (Rv. 10)	Depósito Fig 3
Estructura (16)	Contenedor	Contenedor (16')
Elemento de retención (6)	Dos elementos de retención (77), (Rv. 5)	Dos elementos de retención (6)

Del problema resuelto por la invención y las anterioridades

La presente solicitud trata de resolver problemas relacionados con la biodisponibilidad de los anticonceptivos o diferentes moléculas que puedan ser entregadas por el dispositivo y la mejora de la velocidad de liberación de las mismas. El problema mencionado se puede ver en la siguiente aparte del documento de prioridad de la solicitud 10-054-915:

[0005] To effectively control the pharmacodynamic properties, a system must be able to store a sufficient dose of agent to ensure a sufficient flux over a prolonged period, yet small enough to prevent injury or pain on passing through the cervix. Another difficulty encountered in manufacturing an IUS is the need to produce a structure that is strong enough to endure the forces of insertion, removal and usage without breaking yet again is small enough to prevent injury or pain on passing through the cervix. In particular, the connection between the arms and the stem must be flexible to allow folding of the arms around or within the inserter. On removal the arms must again fold without breaking off, since loss of part of the device within the uterus could lead to complications. One device that attempts to solve these problems is shown in US7080647, in which arms are attached to a slot in a medicated fibre stem. The strength of the device appears to be dependent upon the limited material available for the slot connection. Another device is known from WO96/01092 in which a medicated deposit is used to form the arms of the device and the stem comprises a loop that encircles the arms.

[0008] It would be desirable to be able to manufacture a simple device in which the release rate of the medication or agent could be easily predicted. The rate should also be reliably maintained in practice. Furthermore, the construction of the device should be simple and involve a minimum number of components and yet be both strong and flexible and small enough to allow easy insertion.

Se anota que **US3656483** trataba el mismo problema revelado por la presente solicitud (Col. 1, líneas 1 a 5), veamos:

"The present invention relates to intrauterine medicator devices and in particular to intrauterine carries of medication for locally supplying medication to the uterine walls. One of the embodiments of the invention is directed to an intrauterine carrier of antifertility agents..."

Por su parte, la anterioridad US4102998 presenta el problema objetivo de la siguiente manera (Col 4, líneas 40 a 50):

"A concomitant object of this invention is to provide an IUD which will release more than one kind of medication into the uterus and/or vagina from a plurality of refillable compartments."

Teniendo en cuenta lo anterior, se observa que para comprender la ventaja técnica y el problema propuesto por la presente solicitud y por las anterioridades, se requieren conocimientos sobre temas de formas liberación prolongada, sostenida, inmediata, desarrollo de SENF las cuales hacen parte de la especialidad de Química Farmacéutica.

Se anota que la evaluación de la presente solicitud no fue precisa, pues el Examinador no contaba con la preparación específica que le permitiera comprender el espíritu de la invención y tampoco el de las anterioridades; por ello, ignoró las partes fundamentales para tomar una decisión sobre estos temas, ya que una persona versada en la materia habría encontrado que NO hay evidencia de la existencia de ejemplos en la descripción que ilustraran la mejor forma de llevar a cabo la invención, ni datos que demuestren la ventaja inesperada o sorprendente lograda por los SIU reclamados por el solicitante.

Como se puede ver, los documentos mencionados por la oposición dentro del trámite son pertinentes y revelan las características técnicas esenciales del dispositivo SIU reclamado por el solicitante. Teniendo en cuenta el cuadro comparativo presentado y la relación del problema técnico abarcado por los tres documentos, se ha demostrado que estos efectivamente daban indicios a la persona medianamente versada en la materia para llegar al diseño del dispositivo médico reclamado.

4. Objeciones sobre la aplicación industrial

Método de tratamiento

A pesar de que el sistema intrauterino del expediente 10-054-915 se refiere en sus reivindicaciones al sistema de Estructura-Depósito y de Método para formar este DIU, se observa que la aplicación de estos son métodos anticonceptivos, sobre lo cual se llama la atención de ese Despacho pues se estaría refiriendo a la modalidad de protección de un método anticonceptivo, lo cual según el MAP no es patentable (Manual Andino de Patentes, p.50):

En relación con el presente tema, merecen atención algunas decisiones de la Oficina Europea de Patentes (OEP) que resultan ilustrativos:

a) Métodos de contracepción

Los métodos de contracepción son a menudo considerados como sin aplicación industrial porque son principalmente utilizados en el área privada de la mujer.

T 74/93 (OJ 1995, 712)

El hecho de que para algunas mujeres la contracepción esté relacionada con actividades profesionales, no confiere un carácter industrial a un acto esencialmente privado y personal. Sin embargo, este principio no se aplica a la contracepción en general, sino sólo a maneras particulares de aplicación del contraceptivo.

Se deja de presente que este tipo de métodos no tienen aplicación industrial.

Por último, como información adicional a la ya aportada, es importante destacar la gran cantidad de artículos científicos recientes relacionados con Sistemas Intrauterinos y el hecho de que los mismos señalan información útil, en su mayoría anterior a la fecha de prioridad invocada por la solicitud colombiana 10-054-915 a saber:

□ Use of evidence-based practices that are both cost-effective and acceptable to patients is now a focus in health care. Considerable cost savings can be realized by reducing unintended pregnancies and improving control of menstrual-related morbidity. The levonorgestrel intrauterine system (LNG-IUS), often referred to by its brand name Mirena, has been approved by the Food and Drug Administration both for contraception and for treating abnormal uterine bleeding. The device has been available in the United States since 2000 and has been used in Europe since 1990. Despite the fact that several evidence-based guidelines include use of the LNG-IUS, it remains underutilized in this country. This article reviews the benefits of the LNG-IUS as they pertain to women's health and to the cost of health care.

*Cost Effectiveness in Obstetrics and Gynecology,
The Levonorgestrel Intrauterine System, March 2012, Minnesota Medicine, p. 51
(...)*

Adolescents and Long-Acting Reversible Contraception: Implants and Intrauterine Devices

ABSTRACT: Long-acting reversible contraception (LARC)—intrauterine devices and the contraceptive implant—are safe and appropriate contraceptive methods for most women and adolescents. The LARC methods are top-tier contraceptives based on effectiveness, with pregnancy rates of less than 1% per year for perfect use and typical use. These contraceptives have the highest rates of satisfaction and continuation of all reversible contraceptives. Adolescents are at high risk of unintended pregnancy and may benefit from increased access to LARC methods.

Adolescents and Long-Acting Reversible Contraception: Implants and Intrauterine Devices, The American College of Obstetricians and Gynecologists women's health care physicians, Committee opinion, Number 539 • October 2012

(...)

... el uso de uno para el control de la fertilidad.

La idea del dispositivo intrauterino es muy antigua, atribuyéndose a Hipócrates la introducción de elementos extraños intrauterinos utilizando un tubo de plomo para tal fin. Existe la leyenda de que los primitivos nómadas colocaban piedras dentro del útero de las camellas para evitar dificultades en los viajes. En 1909, el alemán Richter usó un dispositivo intrauterino (DIU), que consistía en una cuerda hecha con tripa de gusano de seda. En 1916, Robert Dickinson utilizó tallos intrauterinos como método anticonceptivo. En 1929, Gräfenberg describió un anillo de metal cuyo uso se discontinuó por las lesiones cervicales que se producían al colocarlo y retirarlo. Posteriormente, el uso de materiales modernos flexibles permitió nuevamente su uso. En 1934, Ishihama y Ota en Japón e Israel, respectivamente, emplearon por primera vez material plástico. En 1959, Margulies en Nueva York, presenta el primer dispositivo asociado a bario, y en 1960, Lippes, en la Universidad de Búfalo, desarrolla un nuevo DIU en forma de doble "S" (Asa de Lippes). En 1963, Jaime Zipper, luego de experiencias en conejas con el DIU de polietileno y

[40]

ANTICONCEPCIÓN PIO IVÁN GOMEZ-2012, p.40

(...)

Over the past decade, intrauterine device (IUD) use by women in the United States has increased from 1.3% of total contraceptive use in 2002 to 8.5% in 2007–2009.¹ Although this increase still does not exceed the nearly 10% rate seen in the 1970s, it does suggest an improving comfort level by physicians and patients alike in choosing this type of long-acting reversible contraception. A better understanding of the reasons behind early discontinuation, the development of new therapeutic uses, and a better appreciation of the low risk of adverse outcomes associated with the IUD has spurred interest in this option not only for contraception but also for therapeutic intervention.² In this issue of *Obstetrics & Gynecology*, we note investigators addressing all three issues regarding the modern use of the levonorgestrel-releasing intrauterine system (see pages 934, 943, and 1091).^{3–5}

The intrauterine device a good thing revisited, Obstetrics & Gynecology, vol. 121, no. 5, may 2013

(...)

Introduction

Intrauterine contraceptive devices (IUDs), including the copper intrauterine device (Cu-IUD-Multiload, Shering Plough and Copper TT380, Medical Industries of Australia) and the levonorgestrel intrauterine system (LNG-IUS; Mirena, Bayer Schering Pharma, Australia) are highly effective methods that have failure rates, which are similar to, or better than, sterilisation.¹ IUD methods are rapidly reversible and will not impact on subsequent fertility unless a woman experiences acute pelvic inflammation around the time of insertion believed to be related to the presence of an underlying, unrecognised sexually transmitted infection (STI).² IUDs are therefore not contraindicated in uninfected nulliparous women.³

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Received 13 July 2009; accepted 10 January 2010.

Importantly, the risk of pelvic infection seems to be confined to the first 20 days after insertion and, in low-risk populations, this is very uncommon.⁴ Both the Cu-IUD and the LNG-IUS have a pre-fertilisation mechanism of action: the Cu-IUD through copper ions having a toxic effect on spermatozoa and the LNG-IUS primarily through progestogen action on cervical mucous and the endometrium.⁵ The copper IUD can also be used for emergency contraception up to five days after unprotected sex and is more effective than oral emergency contraceptive pills in preventing pregnancy.⁶

During the last five years, the growth in popularity of the LNG-IUS has re-ignited interest in intrauterine methods. Nevertheless, in Australia, they remain a relatively uncommon contraceptive choice, with published data from 2002 suggesting that only 2% of women were using them. However, with increased uptake of the LNG-IUS, the figure is likely to be around 5% in 2009.^{7,8} In contrast, 7% of British women⁹ and 23% of women in Norway¹⁰ rely on IUDs for contraception. The reasons for these differences are not known, but it is likely that reluctance to use the methods may result from a lack of understanding of recent evidence.⁴ The 1970s class actions against the manufacturers

A study investigating obstetricians' and gynaecologists' management of women requesting an intrauterine device, Journal compilation, The Royal Australian and New Zealand College of Obstetricians and Gynaecologists, p. 184

Introduction

Intrauterine contraceptive device (IUCD) is an effective and convenient contraceptive method which has failed to gain adequate acceptance because the presently available inert and copper releasing intrauterine devices increase the menstrual blood loss sometimes to such an extent as to cause iron deficiency anemia^{1,2}. In developed countries women with adequate nutrition may make up for this blood loss but those with higher prevalence of anemia are at serious health risks due to the increased blood loss.

The recognition of the favorable effect of oral steroid contraception on the amount of menstrual blood loss has been part of the basis for development of a steroid releasing intrauterine device. Levonorgestrel intrauterine system (LNG), Mirena[®] (Schering Pharmaceuticals, Hong Kong, China) is a T-shaped intrauterine device with a cylinder containing levonorgestrel which releases 20 microgram of levonorgestrel in 24 hours through a release rate controlling membrane³ and is effective for a duration of 5 years with proven efficacy. The IUCD is aimed at reducing some of the problems related to the copper releasing intrauterine devices. The present study was conducted to compare the effects of levonorgestrel

Comparison of levonorgestrel and copper releasing intrauterine contraceptive device on body iron stores and menstrual bleeding patterns: experience on Indian women, European Review for Medical and Pharmacological Sciences, 2012, p. 230

Para terminar y habida cuenta de los planteamientos formulados a lo largo de este escrito, solicito comedidamente a este Despacho revoque la decisión de concesión y practique un nuevo examen de patentabilidad, en esta ocasión, a través de un examinador técnico con conocimientos en Química Farmacéutica con el fin de evaluar la pertinencia de éste recurso y los argumentos presentados por ésta firma a lo largo del trámite, así mismo, se solicita el Despacho decrete, además de la negación de la solicitud en comento, el archivo del expediente que lo contiene.

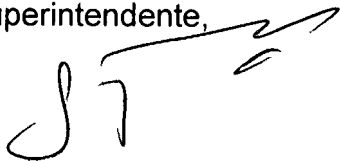
III. PRUEBAS

Ruego que se tenga como tal, sin perjuicio de aquellas que el Despacho considere oficiosamente, las siguientes:

- Ficha del Medicamento MIRENA Dispositivo intrauterino 20mcg/24h: Autorización de comercialización, diciembre 2006.
- Cost Effectiveness in Obstetrics and Gynecology The Levonorgestrel Intrauterine System; Mattson, Lisa; March 2012; Clinical & health affairs; Minnesota Medicine, p. 51

- Adolescents and Long-Acting Reversible Contraception: Implants and Intrauterine Devices; The American College of Obstetricians and Gynecologists, Committee opinion, Number 539, October 2012, p. 983.
- Anticoncepción, Gómez, Pío Iván -2012, p.40
- The intrauterine device a good thing revisited, Obstetrics & Gynecology, Soper, David E., vol. 121, no. 5, may 2013, p.919
- A study investigating obstetricians' and gynaecologists' management of women requesting an intrauterine device, Kirsten I. Black, Journal compilation, The Royal Australian and New Zealand College of Obstetricians and Gynaecologists, 2010, p. 184
- Comparison of levonorgestrel and copper releasing intrauterine contraceptive device on body iron stores and menstrual bleeding patterns: experience on Indian women, European Review for Medical and Pharmacological Sciences, 2012, p. 230

Señor Superintendente,



JOSE LUIS REYES VILLAMIZAR

C.C. 79.152.473 de Usaquén
T.P. 44655 del C. S de la J.

Ficha del Medicamento MIRENA Dispositivo intrauterino 20 mcg/24 h

RESUMEN

LAB: BAYER

ATC: Anticonceptivos intrauterinos

Composición

Levonorgestrel 52 mg

Indicaciones

Anticoncepción femenina, Menorragia idiopática

Posología

Insertar en la cavidad uterina, siendo eficaz durante 5 años. Tasa inicial de liberación: 20 mcg/día, reduciéndose a 11 mcg/día después de 5 años; tasa media de disolución 14 mcg/día hasta los 5 años

Presentación y Precio

Env. con 1; € 164,06. Diagnóstico hospitalario; dispensación sujeta a prescripción médica.

COMPOSICIÓN CUALITATIVA Y CUANTITATIVA

Principio activo: Cada sistema de liberación intrauterino contiene 52 mg de levonorgestrel. La tasa inicial de liberación es de 20 microgramos / 24 h.

Para la lista completa de excipientes, ver apartado *Lista de excipientes*.

FORMA FARMACÉUTICA

Sistema de liberación intrauterino (SLI).

El SLI de levonorgestrel (LNG) está formado por un núcleo blanco o casi blanco, recubierto por una membrana opaca, situado sobre la parte vertical de un cuerpo en forma de T. El cuerpo en forma de T presenta un asa en uno de los extremos de la parte vertical y dos brazos horizontales en el otro extremo. Los hilos de extracción se encuentran unidos al asa. La parte vertical del SLI se introduce en el tubo de inserción, en el extremo del insertor. El SLI y el insertor se encuentran libres esencialmente de impurezas visibles.

DATOS CLÍNICOS

Las evaluaciones preclínicas de seguridad no mostraron riesgos especiales para los seres humanos en base a los estudios de seguridad farmacológicos, de toxicidad, de genotoxicidad y de potencial carcinogénico de levonorgestrel. Levonorgestrel es un progestágeno ampliamente conocido con actividad antiestrogénica. El perfil de seguridad tras administración sistémica está bien documentado. Un estudio en monos a los que se les administró levonorgestrel por vía intrauterina durante 12 meses, confirmó la actividad farmacológica local con buena tolerancia y sin presentar signos de toxicidad sistémica. No se observó embriotoxicidad en conejos tras administración intrauterina de levonorgestrel. La evaluación de seguridad de los componentes elastómeros del reservorio hormonal, de los materiales de polietileno del producto y de la combinación de elastómero y levonorgestrel, basada tanto en la valoración de la toxicología genética, mediante pruebas estándar *in vivo* e *in vitro*, como en ensayos de biocompatibilidad en ratones, cobayas, conejos y sistemas de evaluación *in vitro*, no reveló incompatibilidad biológica.

DATOS CLÍNICOS / INDICACIONES TERAPÉUTICAS

Anticoncepción.

Menorragia idiopática.

DATOS CLÍNICOS / POSOLOGÍA

Mirena se inserta en la cavidad uterina, siendo eficaz durante 5 años.

La tasa de disolución *in vivo* es de aproximadamente 20 microgramos / 24 horas inicialmente, reduciéndose a aproximadamente 11 microgramos / 24 horas después de 5 años. La tasa media de disolución de levonorgestrel es de aproximadamente 14 microgramos / 24 horas hasta los 5 años.

• Inserción y retirada/sustitución

En mujeres en edad fértil, Mirena tiene que insertarse en la cavidad uterina en un plazo de 7 días a partir del inicio de la menstruación. Mirena puede reemplazarse por un sistema nuevo en cualquier momento del ciclo menstrual. El sistema también puede ser insertado inmediatamente después de un aborto producido durante el primer trimestre.

Las inserciones postparto deben posponerse hasta que el útero haya involucionado completamente, pero no antes de transcurridas 6 semanas del parto. Si la involución se retrasase considerablemente habría que valorar el esperar hasta las 12 semanas postparto. En caso de una inserción complicada y/o dolor o sangrado excepcional durante o después de la inserción, se deberá realizar inmediatamente un reconocimiento médico y una ecografía para excluir la perforación.

Se recomienda que Mirena sea insertado solamente por médicos/profesionales sanitarios que tengan experiencia en inserciones de Mirena y/o hayan recibido la formación adecuada para insertar Mirena.

Mirena se retira tirando suavemente de los hilos de extracción con un forceps. Si los hilos no fueran visibles y el sistema estuviera en la cavidad uterina, éste podría retirarse mediante unas pinzas de tenáculo estrechas. Esta maniobra puede requerir la dilatación del canal cervical.

El sistema debe retirarse transcurridos 5 años. Si la usuaria deseara continuar usando el mismo método, se podría insertar en ese momento un nuevo sistema.

Si no se desea un embarazo, en mujeres en edad fértil, el sistema se retirará durante la menstruación, a condición de que ésta corresponda a un ciclo menstrual. Si el sistema se retirase durante los días centrales del ciclo y la usuaria hubiese mantenido relaciones sexuales durante la semana anterior, se debe considerar el riesgo de embarazo a no ser que se inserte un nuevo sistema inmediatamente después de la retirada del anterior.

DATOS CLÍNICOS / CONTRAINDICACIONES

Embarazo o sospecha del mismo;

Enfermedad inflamatoria pélvica actual o recurrente;

Infección del tracto genital inferior;

Endometritis postparto;

Aborto séptico en los últimos tres meses;

Cervicitis;

Displasia cervical;

Tumor maligno uterino o cervical;

Tumores dependientes de progestágenos;

Hemorragias uterinas anormales no diagnosticadas;

Anomalías uterinas congénitas o adquiridas, como miomas si estos deforman la cavidad uterina;

Situaciones en las que exista una mayor susceptibilidad a contraer infecciones;

Enfermedad hepática aguda o tumor hepático;

Hipersensibilidad a levonorgestrel o a alguno de los excipientes.

DATOS CLÍNICOS / ADVERTENCIAS Y PRECAUCIONES

Mirena debe emplearse con precaución tras consultar al especialista y se debe considerar la retirada del sistema en caso de existencia o aparición por primera vez de alguna de las siguientes situaciones:

- Migraña, migraña focal con pérdida asimétrica de visión u otras alteraciones que indiquen isquemia cerebral transitoria
- Cefaleas de intensidad excepcionalmente grave
- Ictericia
- Marcado incremento de la presión sanguínea
- Enfermedades arteriales graves tales como ictus o infarto de miocardio

Algunos estudios epidemiológicos recientes mostraron que, en mujeres que utilizan anticonceptivos orales con progestágeno exclusivamente, puede existir un ligero incremento del riesgo de padecer tromboembolismo venoso, aunque los resultados no fueron estadísticamente significativos. No obstante, si se produjesen síntomas o signos de trombosis se deberían instaurar de forma inmediata medidas diagnósticas y terapéuticas adecuadas. Los síntomas de trombosis arterial o venosa pueden incluir: dolor y/o edema unilateral en extremidades inferiores; dolor torácico grave y repentino, irradie o no al brazo izquierdo; disnea súbita; aparición súbita de tos; cualquier cefalea inusual, grave y prolongada; pérdida repentina de la visión, parcial o completa; diplopia; habla confusa o afasia; vértigo; colapso con o sin crisis convulsiva focal; debilidad o entumecimiento muy marcado que de forma súbita afecte a un lado o parte del cuerpo; alteraciones motoras; abdomen "agudo". Los síntomas o signos que indican trombosis retiniana son: pérdida inexplicable parcial o completa de la visión; aparición de proptosis o diplopia; edema papilar o lesiones vasculares de la retina.

No existe consenso sobre el posible papel de las venas varicosas y la tromboflebitis superficial en el tromboembolismo venoso.

Mirena debe ser usado con precaución en mujeres que presenten enfermedad cardíaca congénita o enfermedad valvular del corazón y riesgo de endocarditis infecciosa. Cuando se inserte o se retire el SLI a estas pacientes debe administrarse profilaxis antibiótica.

Dosis bajas de levonorgestrel pueden afectar a la tolerancia a la glucosa, por ello, en usuarias de Mirena diabéticas se debe controlar la glucemia. No obstante, por lo general no es necesario alterar la pauta terapéutica en usuarias de Mirena diabéticas.

Las hemorragias irregulares pueden enmascarar algunos signos y síntomas de poliposis endometrial o cáncer de endometrio, por lo que en estos casos deben establecerse las medidas diagnósticas apropiadas.

Mirena no es el método de primera elección para mujeres nuligrávidas.

Un meta-análisis de 54 estudios epidemiológicos mostró que existe un ligero aumento del riesgo relativo ($RR = 1.24$) de padecer cáncer de mama en mujeres que están usando anticonceptivos combinados orales (AOC), principalmente los preparados de estrógeno-progestágeno. Este aumento del riesgo desaparece gradualmente en un periodo de 10 años tras la suspensión de los AOC. Debido a que el cáncer de mama es raro en mujeres menores de 40 años, el aumento del número de diagnósticos de cáncer de mama en usuarias, que toman AOC en el momento actual o que los han tomado recientemente, es pequeño en comparación al riesgo total de padecer cáncer de mama. El riesgo de presentar cáncer de mama en usuarias de minipíldoras es posiblemente de la misma magnitud que el asociado con AOCs. No obstante, para los preparados a base de progestágenos exclusivamente, la evidencia está basada en poblaciones mucho menores de usuarias y por ello es menos concluyente que para los AOCs. Estos estudios no aportan datos de causalidad. El patrón observado de aumento de riesgo puede deberse a un diagnóstico precoz del cáncer de mama en usuarias de AOC, a efectos biológicos de éstos o a una combinación de ambos factores. Los cánceres de mama diagnosticados en usuarias tienden a estar menos avanzados clínicamente que los diagnosticados en nuevas usuarias.

- Exploración / consulta médica

Previamente a la inserción, debe informarse a la usuaria de la eficacia, riesgos y efectos secundarios de Mirena. Se debe realizar una exploración física, incluyendo tacto vaginal, exploración de las mamas y citología cervical. Debe descartarse la existencia de embarazo y la presencia de enfermedades de transmisión sexual, y tratarse de forma satisfactoria las infecciones genitales. Se deberán determinar el tamaño de la cavidad uterina y la posición del útero. Es especialmente importante el situar Mirena en posición fúndica para así asegurar una exposición homogénea del endometrio al progestágeno, prevenir la expulsión y obtener la máxima eficacia. Por tanto, se han de seguir atentamente las instrucciones de inserción. Ya que la técnica de inserción es diferente a la de otros dispositivos intrauterinos, debe hacerse un énfasis especial en el aprendizaje de la técnica de inserción correcta. La inserción y la retirada pueden asociarse a la aparición de algo de dolor y sangrado. El procedimiento puede precipitar un desmayo por reacción vasovagal o la aparición de una crisis en pacientes epilépticas.

Debería efectuarse una revisión a las 4 - 12 semanas de la inserción y con posterioridad una vez al año,

o con mayor frecuencia si estuviera clínicamente indicado.

Mirena no debe emplearse como anticonceptivo postcoital.

Debido a que la aparición de hemorragias irregulares y/o manchado es común durante los primeros meses de tratamiento, se recomienda descartar la existencia de patología endometrial antes de la inserción de Mirena. Si la mujer continua con el uso de Mirena, insertado previamente para anticoncepción, debe excluirse la patología endometrial si aparecen sangrados irregulares tras el comienzo de la terapia de sustitución estrogénica. Si aparecieran sangrados irregulares durante un tratamiento prolongado, deberían instaurarse las medidas diagnósticas apropiadas.

- Oligo/amenorrea

En aproximadamente un 20% de las usuarias en edad fértil se desarrolla gradualmente una oligomenorrea o amenorrea. De no producirse menstruación en el plazo de 6 semanas tras el comienzo de la menstruación previa, debe considerarse la posibilidad de embarazo. No es necesaria la repetición de la prueba de embarazo en usuarias amenorreicas a no ser que aparezcan otros síntomas de embarazo.

- Infección pélvica

El tubo de inserción ayuda a prevenir la contaminación de Mirena por microorganismos durante la inserción ya que el insertor de Mirena ha sido diseñado para reducir al mínimo el riesgo de infecciones. En las usuarias de dispositivos intrauterinos de cobre, la tasa más elevada de infecciones pélvicas se produce durante el primer mes después de la inserción y disminuye posteriormente. Algunos estudios sugieren que el índice de infecciones pélvicas en las usuarias de Mirena es menor que el observado con los dispositivos intrauterinos liberadores de cobre. La multiplicidad de parejas sexuales es un factor de riesgo conocido para la enfermedad inflamatoria pélvica. La infección pélvica puede tener serias consecuencias, perjudicar la fertilidad e incrementar el riesgo de embarazo ectópico.

Debe retirarse Mirena si la mujer experimenta endometritis recurrente, infecciones pélvicas o en caso de que una infección aguda sea grave o no responda a los pocos días al tratamiento.

Se recomienda realizar exámenes bacteriológicos y monitorización incluso cuando los síntomas indicativos de infección sean discretos.

- Expulsión

El dolor y el sangrado pueden ser síntomas de la expulsión parcial o completa de cualquier DIU. Sin embargo, un dispositivo puede ser expulsado de la cavidad uterina sin que la mujer sea consciente de ello. La expulsión parcial puede disminuir la eficacia de Mirena. Dado que Mirena disminuye el volumen del flujo menstrual, un incremento de éste puede ser indicativo de expulsión.

Un Mirena desplazado debe retirarse, pudiendo insertarse uno nuevo en ese momento.

Debe instruirse a la usuaria en cómo verificar la situación de los hilos de extracción de Mirena.

- Perforación

En raras ocasiones, más frecuentemente durante la inserción, puede producirse la perforación o penetración del cuerpo o cérvix uterinos por un anticonceptivo intrauterino. En esos casos el sistema debe ser retirado. El riesgo de perforación puede aumentar con las inserciones postparto (ver sección *Posología y forma de administración*), en mujeres lactantes y en mujeres con el útero en retroversión.

- Embarazo ectópico

El riesgo de embarazo ectópico es mayor en mujeres con antecedentes de este tipo de embarazo, cirugía tubárica o infección pélvica. Se debería considerar la posibilidad de un embarazo ectópico en caso de dolor en la zona inferior del abdomen, especialmente si se presenta acompañado de amenorrea

o sangrado en mujeres amenorreicas. La tasa de embarazo ectópico en usuarias de Mirena es de 0,06 por 100 mujeres-año. Esta tasa es más baja que el 0,3-0,5 por 100 mujeres-año que se estima para mujeres no usuarias de ningún método anticonceptivo. El riesgo absoluto de embarazo ectópico en usuarias de Mirena es bajo. No obstante, cuando una mujer se queda embarazada con Mirena *in situ*, la probabilidad relativa de embarazo ectópico aumenta.

- Pérdida de los hilos de extracción

Si los hilos de extracción no se visualizan en el cérvix en los reconocimientos de control, debe excluirse la existencia de embarazo. Los hilos podrían haberse introducido en el canal cervical o en el útero, pudiendo reaparecer en la siguiente menstruación. Una vez descartada la posibilidad de embarazo, normalmente se pueden localizar los hilos explorando cuidadosamente con el instrumental adecuado. Si éstos no se localizan, el sistema puede haber sido expulsado. Para verificar la correcta posición del sistema puede emplearse el diagnóstico ecográfico. Si no se dispusiera de éste o no se tuviera éxito, pueden utilizarse técnicas radiográficas para localizar Mirena.

- Atresia folicular retardada

Puesto que el efecto anticonceptivo de Mirena se debe principalmente a su acción local, es habitual que se produzcan ciclos ovulatorios con rotura folicular en mujeres en edad fértil. En algunas ocasiones la atresia del folículo se retrasa y la foliculogénesis puede continuar. Estos folículos aumentados son indistinguibles clínicamente de los quistes ováricos. Los folículos aumentados se han diagnosticado en aproximadamente un 12% de las usuarias de Mirena. La mayoría de estos folículos son asintomáticos, aunque en ocasiones pueden acompañarse de dolor pélvico o dispareunia.

En la mayoría de los casos, los folículos aumentados desaparecen espontáneamente en un plazo de dos a tres meses de observación. Si esto no ocurriera, se recomienda continuar el seguimiento mediante ecografía y otras medidas diagnósticas o terapéuticas. Sólo en raras ocasiones puede ser necesaria la intervención quirúrgica.

- Información relevante sobre algunos de los componentes de Mirena

La estructura en forma de T de Mirena contiene sulfato de bario, que lo hace visible en caso de un reconocimiento por rayos X.

DATOS CLÍNICOS / INTERACCIONES

El metabolismo de los progestágenos puede verse aumentado por el uso concomitante de sustancias inductoras de las enzimas metabolizadoras de fármacos, en concreto las enzimas del citocromo P450, como los anticonvulsivantes (p. ej., fenobarbital, fenitoína, carbamacepina) y los antiinfecciosos (p. ej., rifampicina, rifabutina, nevirapina, efavirenz). No se conoce la influencia de estos fármacos sobre la eficacia anticonceptiva de Mirena, pero no se cree que revista mayor importancia ya que el mecanismo de acción de éste es principalmente local.

DATOS CLÍNICOS / EMBARAZO Y LACTANCIA

- Embarazo

Mirena está contraindicado en caso de embarazo o sospecha del mismo. En caso de embarazo accidental con Mirena se recomienda la retirada del sistema, dado que la permanencia *in situ* de cualquier anticonceptivo intrauterino puede incrementar el riesgo de aborto y de parto pretérmino. La retirada de Mirena o la exploración del útero pueden dar lugar a un aborto espontáneo. Si el anticonceptivo intrauterino no puede retirarse con suavidad debería considerarse la interrupción del embarazo. Si la mujer deseara continuar la gestación y el sistema no pudiera ser retirado, debe informársele sobre los riesgos y las posibles consecuencias para el neonato de un parto prematuro. El desarrollo de dicha gestación debe vigilarse cuidadosamente. Debe excluirse la presencia de embarazo ectópico. Debe instruirse a la mujer para que informe de cualquier síntoma que indique complicaciones de la gestación, tales como el dolor espástico abdominal con fiebre.

Debido a la administración intrauterina y a la exposición local a la hormona, no puede excluirse por completo la posibilidad de teratogenicidad (especialmente virilización). La experiencia clínica sobre el resultado de embarazos habidos con Mirena es limitada, debido a la elevada eficacia anticonceptiva. No obstante, debe informarse a la mujer que, hasta la fecha, no hay evidencia de defectos congénitos asociados al empleo de Mirena en los casos en que la gestación se ha llevado a término con Mirena *in situ*.

- Lactancia

La dosis diaria de levonorgestrel y las concentraciones en sangre son menores con Mirena que con cualquier otro anticonceptivo hormonal, aunque se ha encontrado levonorgestrel en la leche materna. Durante la lactancia no se recomiendan los anticonceptivos hormonales como método de primera elección, considerándose los métodos basados exclusivamente en progestágenos de segunda elección, después de los métodos anticonceptivos no hormonales.

No parecen existir efectos deletéreos sobre el crecimiento y desarrollo infantil cuando se emplea cualquier método basado exclusivamente en progestágenos tras seis semanas postparto. Los métodos basados exclusivamente en progestágenos no parecen afectar a la cantidad ni a la calidad de la leche materna.

DATOS CLÍNICOS / EFECTOS SOBRE LA CAPACIDAD DE CONDUCIR

Se desconocen.

DATOS CLÍNICOS / REACCIONES ADVERSAS

Las reacciones adversas son más frecuentes durante los primeros meses tras la inserción, desapareciendo con el empleo prolongado. En usuarias de Mirena, además de las reacciones adversas enumeradas en la sección *Advertencias y precauciones especiales de empleo*, se han notificado las siguientes:

Entre las reacciones adversas muy frecuentes (ocurren en más del 10% de las usuarias) se encuentran el sangrado uterino/vaginal, que incluye manchado, oligomenorrea, amenorrea, y los quistes benignos de ovario.

En mujeres fértiles, el número medio de días de manchado/mes disminuye gradualmente de nueve a cuatro días durante los seis primeros meses de uso. El porcentaje de mujeres con sangrado prolongado (más de ocho días) disminuye de un 20% a un 3% durante los tres primeros meses de uso. En ensayos clínicos, durante el primer año de empleo, un 17% de las mujeres experimentó amenorrea de al menos tres meses de duración.

La frecuencia de quistes benignos de ovario depende del método diagnóstico usado. En ensayos clínicos se han diagnosticado folículos aumentados de tamaño en el 12% de las usuarias de Mirena. La mayoría de estos folículos son asintomáticos y desaparecen en tres meses.

La siguiente tabla enumera las reacciones adversas mediante el *MedDRA system organ classes* (MedDRA SOCs). Las frecuencias están basadas en datos de ensayos clínicos

Sistema orgánico	Frecuencia de las reacciones adversas		
	Frecuentes ≥ 1/100, < 1/10	Poco frecuentes ≥ 1/1.000, < 1/100	Raras ≥ 1/10.000, < 1/1.000
Trastornos psiquiátricos	Ánimo depresivo, nerviosismo, disminución de la libido	Labilidad emocional	
Trastornos del sistema nervioso	Cefaléa	Migraña	
Trastornos gastrointestinales	Dolor abdominal, náuseas	Distensión abdominal	
Trastornos de la piel y del tejido subcutáneo	Acné	Alopecia, hirsutismo, prurito, eczema	Rash, urticaria
Trastornos musculoesqueléticos y del tejido conjuntivo	Dolor de espalda		
Trastornos del aparato reproductor y de la mama	Dolor pélvico, dismenorrea, flujo vaginal, vulvovaginitis, tensión mamaria, mastalgia, expulsión del SIL	Enfermedad inflamatoria pélvica, endometritis, cervicitis/frotis de Papanicolau normal, clase II	Perforación uterina
Trastornos generales y alteraciones en el lugar de administración		Edema	
Exploraciones complementarias	Aumento de peso		

El término MedDRA más adecuado se utiliza para describir una determinada reacción y sus sinónimos y trastornos relacionados.

Cuando una mujer se queda embarazada con Mirena *in situ*, aumenta el riesgo relativo de embarazo ectópico. Además se han comunicado casos de cáncer de mama (frecuencia desconocida, ver sección *Advertencias y precauciones especiales de empleo*).

DATOS CLÍNICOS / SOBREDOSIFICACIÓN

No aplicable.

PROPIEDADES FARMACOLÓGICAS / PROPIEDADES FARMACODINÁMICAS

Grupo farmacoterapéutico: DIU plásticos con progestágenos

Código ATC: G02BA03

Levonorgestrel es un progestágeno empleado en ginecología de diferentes formas: como componente progestagénico en los anticonceptivos orales y en la terapia hormonal sustitutiva, o aisladamente para la anticoncepción en las mini-píldoras y en implantes subdérmicos. Mediante un sistema de liberación intrauterino, levonorgestrel también puede liberarse directamente en la cavidad uterina. Esta última forma permite una dosis diaria muy baja ya que la hormona es liberada directamente al órgano diana.

Mirena presenta principalmente efecto progestativo local en la cavidad uterina. Las altas concentraciones de levonorgestrel en el endometrio disminuyen los receptores endometriales de estrógenos y progesterona, haciendo el endometrio insensible al estradiol circulante y observándose un fuerte efecto antiproliferativo. Durante el empleo de Mirena se observan cambios morfológicos del endometrio y una débil reacción local de cuerpo extraño. El espesamiento del moco cervical previene el paso del esperma a través del canal cervical. El medio local del útero y de las trompas inhibe la motilidad y funcionalidad espermáticas, previniendo la fertilización. En algunas mujeres se inhibe la ovulación.

Los estudios de eficacia anticonceptiva se han realizado principalmente comparando Mirena con diferentes dispositivos intrauterinos de cobre. Hasta el momento, estos incluyen 13.000 mujeres/año que usan Mirena, con una tasa global de embarazos de 0,16 por 100 mujeres/año.

El empleo de Mirena no altera la fertilidad futura. Aproximadamente el 80% de las mujeres con deseo de quedarse embarazadas, concibieron dentro de los 12 meses siguientes a la retirada del sistema.

El patrón de sangrado resulta de la acción directa del levonorgestrel sobre el endometrio y no refleja el ciclo ovárico. No hay diferencias claras en lo referente al desarrollo folicular, la ovulación y la producción de progesterona y estradiol entre las usuarias con diferentes patrones de sangrado. Puede haber un incremento inicial del manchado durante los primeros meses de empleo durante el proceso de inactivación de la proliferación endometrial. Posteriormente, durante el empleo de Mirena, la potente supresión del endometrio da lugar a una reducción de la duración y cantidad del sangrado menstrual. Un flujo menstrual escaso frecuentemente desemboca en una oligomenorrea o amenorrea. La función ovárica es normal y los niveles de estradiol son mantenidos, incluso en usuarias amenorreicas.

Mirena puede emplearse con éxito en el tratamiento de la menorragia idiopática. El volumen del sangrado menstrual disminuyó un 88% en mujeres menorrágicas tras tres meses de empleo. La menorragia causada por miomas submucosos puede responder de forma menos favorable. La reducción en el sangrado incrementa la concentración de hemoglobina en sangre. Mirena también alivia la dismenorrea.

PROPIEDADES FARMACOLÓGICAS / PROPIEDADES FARMACOCINÉTICAS

Tras la inserción de Mirena, la tasa inicial de liberación de levonorgestrel hacia la cavidad uterina es de 20 microgramos/24 horas. Así, se proporciona una concentración plasmática de levonorgestrel estable que, transcurridas las primeras semanas tras la inserción, se estabiliza a niveles de 0,4-0,6 nmol/l (150-200 pg/ml) en mujeres en edad fértil. Después de periodos de empleo de larga duración: 12, 24 y 60 meses, en mujeres jóvenes, las concentraciones plasmáticas de levonorgestrel fueron de 180 ± 66 pg/ml, 192 ± 140 pg/ml y 159 ± 60 pg/ml respectivamente. Debido a los bajos niveles alcanzados en plasma, los efectos sistémicos del progestágeno son mínimos.

La farmacocinética de levonorgestrel ha sido ampliamente estudiada y referenciada en la literatura. Tras la administración oral de levonorgestrel, éste es rápida y completamente absorbido dando lugar a una biodisponibilidad absoluta de aproximadamente un 90%. Levonorgestrel se fija a la albúmina sérica y a la globulina fijadora de hormonas sexuales (SHBG). La distribución relativa (libre, unido a albúmina, unido a SHBG) depende de las concentraciones de SHBG en suero. Tan sólo aproximadamente un 2,5% del total de los niveles de levonorgestrel sérico se encuentra como esteroide libre, mientras que un 47,5% y un 50% están unidos a SHBG y albúmina, respectivamente. Se ha descrito que el volumen medio de distribución para el levonorgestrel es de aproximadamente 137 litros, con una tasa de aclaramiento sérico de 5,7 L/h. La semivida plasmática de eliminación del levonorgestrel, observada tras administración única, está en un rango de 14 a 20 horas. Levonorgestrel se excreta como metabolitos, en aproximadamente igual proporción, en orina y heces. Los metabolitos tienen débil o ninguna actividad farmacológica. El principal metabolito en orina es el tetrahidronorgestrel, que supone aproximadamente el 10% de la radiactividad recuperada en la orina tras la administración de levonorgestrel marcado radiactivamente.

Aproximadamente un 0,1% de la dosis materna de levonorgestrel puede transferirse al lactante por la leche materna.

DATOS FARMACÉUTICOS / LISTA DE EXCIPIENTES

Elastómero de polidimetilsiloxano

Sílice coloidal anhidra

Polietileno

Sulfato de bario

Óxido de hierro

DATOS FARMACÉUTICOS / INCOMPATIBILIDADES

No procede.

DATOS FARMACÉUTICOS / PERÍODO DE VALIDEZ

3 años

DATOS FARMACÉUTICOS / ALMACENAMIENTO

Ninguna.

Mirena se presenta en un envase esterilizado que no debe abrirse hasta el momento de la inserción. El producto, una vez expuesto, debe ser manejado en condiciones de asepsia. Si el sellado del envase estéril estuviera roto, el sistema intrauterino de liberación deberá desecharse.

La eliminación del medicamento no utilizado y de todos los materiales que hayan estado en contacto con él, se realizará de acuerdo con las normativas locales.

DATOS FARMACÉUTICOS / CONTENIDO DEL ENVASE

El producto se presenta empaquetado de forma individual, en un envase blíster termoformado con una cubierta despegable.

AUTORIZACIÓN DE COMERCIALIZACIÓN / TITULAR DE LA AUTORIZACIÓN

Química Farmacéutica Bayer, S.L.

Av.Baix Llobregat 3-5

08970 Sant Joan Despí (Barcelona)

AUTORIZACIÓN DE COMERCIALIZACIÓN / NÚMERO DE LA AUTORIZACIÓN

63.158

AUTORIZACIÓN DE COMERCIALIZACIÓN / FECHA DE LA PRIMERA AUTORIZACIÓN

12 de Diciembre de 2001 / 12 de Diciembre de 2006

AUTORIZACIÓN DE COMERCIALIZACIÓN / FECHA DE REVISIÓN DEL TEXTO

Diciembre 2006

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Cost Effectiveness in Obstetrics and Gynecology

The Levonorgestrel Intrauterine System

By Lisa Mattson, M.D., FACOG

□ Use of evidence-based practices that are both cost-effective and acceptable to patients is now a focus in health care. Considerable cost savings can be realized by reducing unintended pregnancies and improving control of menstrual-related morbidity. The levonorgestrel intrauterine system (LNG-IUS), often referred to by its brand name Mirena, has been approved by the Food and Drug Administration both for contraception and for treating abnormal uterine bleeding. The device has been available in the United States since 2000 and has been used in Europe since 1990. Despite the fact that several evidence-based guidelines include use of the LNG-IUS, it remains underutilized in this country. This article reviews the benefits of the LNG-IUS as they pertain to women's health and to the cost of health care.

It is estimated that 49% of pregnancies in the United States are unintended.¹ In half, women were using some form of birth control during the month before conception.¹ Clearly, there is a need for better methods of contraception. Because long-acting reversible contraceptives eliminate the need for women to remember to take a daily pill or interrupt intercourse, they hold great promise for decreasing the number of unintended pregnancies. Long-acting reversible contraceptives include IUDs and contraceptive implants. These devices require insertion and removal by a health care provider. Once in place, they provide contraceptive benefits for three to 10 years.

The Institute of Medicine has suggested that methods for decreasing unintended pregnancies be included in a list of national priorities for comparative effectiveness research, as health care costs related to pregnancy are significant.² In 2009, the U.S. Agency for Healthcare Research and Quality reported the aver-

age facility charge for labor and delivery in Minnesota ranged from \$8,094 for an uncomplicated vaginal birth to \$20,301 for a complicated delivery via cesarean-section.³ These figures do not include the cost of anesthesia services, additional newborn care, or additional maternal provider charges. There also are significant socioeconomic consequences of an unintended pregnancy, especially for adolescents or unemployed women. It behooves us all to minimize the number of unintended pregnancies and to do so in an effective, affordable, and patient-centered manner. Use of long-acting reversible contraceptives may help move us toward this goal.

The Levonorgestrel Intrauterine System

The levonorgestrel intrauterine system (LNG-IUS), often referred to by its brand name Mirena, is just one of the long-acting reversible contraceptives available to women. It has a T-shaped polyethylene frame that releases 20 µg

of progestin (levonorgestrel) daily for up to five years. This hormone works within the uterine cavity, with minimal systemic absorption. Most women using the LNG-IUS feel the way they would if they were not on any hormonal birth control. Although we still do not understand its exact mechanism of action, LNG-IUS is believed to exert its effects preconceptually to prevent fertilization.⁴ The presence of the IUD promotes a foreign-body reaction within the uterine cavity, creating an environment that is hostile to sperm and ova.⁴⁻¹⁰ Studies have failed to detect any transient increases in human chorionic gonadotropin,^{11,12} and tubal flushing has not identified sperm or fertilized eggs in the fallopian tubes of IUD users.^{8,10} In addition, progestins are known to thicken cervical mucus and prevent the passage of sperm,^{13,14} and invoke histologic changes in the endometrium that serve to inactivate the endometrial lining and keep it thin.^{15,16} Pregnancy rates with LNG-IUS are similar to those with tubal ligation at 1/1,000 to 5/1,000.^{4,17} Contraceptive benefits are realized immediately, and the LNG-IUS can be removed at any time by a qualified health care provider if pregnancy is desired or the patient cannot tolerate the device for any reason. After five years, it should be removed. A new one can be inserted immediately.

The LNG-IUS is an excellent option for women who have trouble remembering to use other forms of birth control such as pills, patches, rings, condoms,

and injectables;¹⁸ women who do not use their birth control properly; women with a contraindication or an aversion to systemic hormones; or women with inadequate access to health care.

Despite evidence that suggests most women are good candidates for the LNG-IUS, it is not widely used. Fears regarding IUDs abound among patients and physicians alike. In the past, IUDs have been linked to increased risk of pelvic inflammatory disease, which increased the risk of female infertility and resulted in malpractice claims. More recent studies have not found any increased risk of infection in IUD users except for a small increased risk during the first 20 days.¹⁹ Other studies have found a decreased risk of progression to pelvic inflammatory disease.²⁰ Thickening of the cervical mucus by the progestin may provide a barrier to ascending infection.

Intrauterine devices have historically been associated with an increased risk of ectopic pregnancy; but data have shown there are fewer ectopic pregnancies among women who use the LNG-IUS compared with women who use no contraception.^{21,22} However, it should be noted that if a pregnancy occurs, it is more likely to be an ectopic and not an intrauterine pregnancy.

There is also no evidence to suggest any increased risk of tubal infertility in users of contemporary IUDs,²⁰ and women can be reassured that there is usually rapid return of fertility following removal of the IUD.²³ For this reason, nulliparous and adolescent women are also considered to be good candidates for an IUD.²⁴

Women with co-existing medical problems often are not good candidates for hormonal contraception, and many of these women need to take special precautions before getting pregnant. Use of an IUD can buy time for women who need to optimize their chances of having a successful pregnancy.

Use of an IUD also can minimize complications or exacerbations of underlying medical problems. It is an excellent choice for women with coagulopathies because it has a minimal impact on hormone levels that may increase the risk of deep

venous thrombosis.²⁵⁻²⁹ It is also ideal for smokers, particularly those older than 35 years of age who have been on hormonal contraception and are seeking an alternate form of birth control. Women with seizure disorders, who are obese, and who have gallbladder disease, hypertension, HIV, and diabetes are also good candidates for this contraceptive method.^{25,26,30}

Successful insertion can usually be accomplished in the office and at any time during the menstrual cycle, assuming a pregnancy test is negative. It is easiest to insert near the end of or right after the patient's period, when the cervix is softer and more pliable. Inserting it after a majority of the endometrium has been sloughed off may also minimize irregular bleeding. Taking ibuprofen prior to insertion can minimize discomfort; in addition, some providers may choose to do a paracervical block to prevent pain. Adolescents and nulliparous women may experience more discomfort; but NSAID use and cervical softening with misoprostol before the appointment may facilitate insertion.^{24,31-33} The IUD also may be inserted after miscarriage, abortion, or immediately postpartum.³⁴

The LNG-IUS is one of the more cost-effective forms of birth control. In one study, only the copper IUD and vasectomy were found to be less expensive.³⁵ In one study involving 1 million women in a California publicly funded family planning program, IUDs and contraceptive implants were found to be the most cost-effective birth control options, with cost savings of \$7 for every \$1 spent on services and supplies.³⁶

The LNG-IUS and Abnormal Uterine Bleeding

Abnormal uterine bleeding is one of the more frequent causes for clinic and emergency department visits by women. It has been estimated that women with abnormal uterine bleeding lose 3.6 weeks of work per year.³⁷ A unique aspect of LNG-IUS is its ability to decrease uterine bleeding. The local effect of progestin decreases endometrial proliferation resulting in decreased bleeding and even amenor-

rhea in some women. Studies have found a 74% to 94% decrease in blood loss, a 0.5 to 1.6 g/dL increase in hemoglobin, and a 50% to 60% decrease in the need for hysterectomy in women who use the LNG-IUS.^{38,39} Although hysterectomy is the definitive treatment for abnormal uterine bleeding, it is more costly and is associated with more serious side effects than LNG-IUS and is irreversible.⁴⁰ Approved by the FDA for abnormal uterine bleeding in 2010, the LNG-IUS improves the user's quality of life, decreases bleeding, preserves reproductive function, and allows her to avoid the risks and costs associated with surgery.

The LNG-IUS also compares favorably with endometrial ablation but costs less. Both endometrial ablation and the LNG-IUS decrease bleeding with comparable patient satisfaction at one year. Whereas, insertion of the LNG-IUD is an in-office procedure that does not require additional equipment, ablation may need to be done at a hospital or outpatient surgery center and requires special equipment and assistance from support staff. In addition, the patient will need to use an additional form of birth control. The cost of the LNG-IUS is difficult to determine, as there is considerable variation across the country; but the American Congress of Obstetricians and Gynecologists recently put the cost of the LNG-IUS at \$703, excluding physician fees.³⁷ An in-office ablation costs roughly \$2,500; the cost increases to nearly \$5,000 when the procedure is done in an ambulatory surgery center. The cost of ablation is more if anesthesia is needed, if a D&C or hysteroscopy is also performed, or if it is combined with a sterilization procedure.

Another more compelling reason to consider the LNG-IUS over ablation is the fact that the IUD can be removed; in such cases, ablation remains an option. If ablation doesn't work, an IUD is no longer an option, and a woman is more likely to need a hysterectomy.

Other Noncontraceptive Benefits of the LNG-IUS

The LNG-IUS's effect on the endometrium may make it an option for treating other gynecologic problems.^{30,38,39} It also has been found to decrease bleeding in women with fibroids and adenomyosis, enough so that it should be considered before proceeding with more expensive treatments or hysterectomy.⁴¹⁻⁴⁴ It may also decrease pain that is associated with periods and reduce retrograde menstrual flow that may be the cause of some of the pain associated with endometriosis.⁴³ Larger studies are needed in these areas; but given the ease of insertion and removal of the IUD, it may be a viable first option, before GnRH agonists and surgery.

Several studies have found evidence that the LNG-IUS decreases the risk of endometrial hyperplasia.⁴⁵ Women with risk factors for endometrial cancer (obesity, hypertension, and diabetes) may benefit from the LNG-IUS if they are in need of birth control and/or reduction in menstrual bleeding. It may also be helpful for women otherwise considering postmenopausal hormone therapy.⁴⁶ The Women's Health Initiative suggested a decreased risk of breast cancer and other health problems in women who were only using estrogen. If the progestin activity in the LNG-IUS decreases the risk of endometrial hyperplasia, it may allow some women to use estrogen only for their menopausal symptoms and decrease their risk for breast cancer, osteoporosis, and colon cancer. The LNG-IUS has not received FDA approval for endometrial protection; but it is approved for this purpose in the United Kingdom.

A recent epidemiological study published in *Lancet Oncology* suggested a reduced risk of cervical cancer among IUD users. Among 20,000 women, there was a strong and consistent inverse relationship between IUD use and cervical cancer. This relationship was not affected by duration of use, with protection at 10 years being comparable to protection at one year. The IUD did not decrease the likelihood of HPV infection among these women, suggesting that the IUD may

interfere with HPV progression to cancer.⁴⁷ It is hypothesized that the reactive, chronic, low-grade inflammatory response that may be responsible for the LNG-IUS's contraceptive mechanism may also be responsible for altering the oncogenic potential of HPV in cervical cells.

Limitations of the LNG-IUS

Not all women will benefit from the LNG-IUS. Since its use does not change the systemic levels of hormones, ovarian function will remain unchanged in premenopausal women. Thus, some women with the IUD may still have significant pain with ovulation. The normal menstrual cycle involves the formation of one or more follicles in the ovary. It is normal for these to measure 2.0 to 2.5 cm; these are considered follicles and not "cysts," which are often interpreted as pathologic.⁴⁸ Ovulation often results in a "blister" on the ovary. This is normal, but if it enlarges or bursts, it can cause pain. Therefore, women with a history of painful ovulation, large ovarian cysts, or with an increased risk of ovarian cancer may benefit more from hormonal contraception that suppresses ovulation.

Women with endometriosis may still have pain as endometrial implants in the pelvis may respond to the estrogen production from the ovaries; and women with significant mood fluctuations related to their cycle or cyclic headaches/migraines may continue to have problems with the LNG-IUS. However, it is possible that the decreased bleeding, decreased cramping, and maintenance of a stable hemoglobin may minimize these cyclic symptoms. The LNG-IUS will decrease bleeding but will not regulate a woman's cycle or make it more predictable. Bleeding will occur at the same time it would have occurred if there was no contraception; but the bleeding should be lighter. Women with the LNG-IUS may still experience perimenopausal symptoms and have hot flashes, night sweats, and mood changes. However, those who have undergone hysterectomy and still have their ovaries, who have undergone endometrial ablation or tubal ligation, or who use any

nonhormonal contraceptive method may also experience some or all of these same symptoms.

Cost is another limitation. Although use of the LNG-IUS appears to be cost-effective, up-front costs make it prohibitive for some smaller clinics to keep it in stock and for some patients to afford. Therefore, efforts need to be made to decrease the initial cost of the device.

Summary

The LNG-IUS has profound potential for improving women's health; yet it is still only used by 6% of women in this country. The evidence has established its cost-effectiveness and utility as a contraceptive and as a tool for reducing abnormal uterine bleeding. Studies continue to find potential advantages for its use in the prevention or treatment of endometriosis, adenomyosis, fibroids, endometrial cancer, and cervical cancer, and in postmenopausal hormone therapy. As health care providers, we need to re-examine what we learned about IUDs in medical school and acquaint ourselves with the benefits of contemporary devices. We then need to pass on our knowledge and help dispel the myths and fears that may exist in our patients' minds in order to provide them with high-quality care.

MM

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The American College of
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WOMEN'S HEALTH CARE PHYSICIANS

COMMITTEE OPINION

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Committee on Adolescent Health Care

Long-Acting Reversible Contraception Working Group

This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

Adolescents and Long-Acting Reversible Contraception: Implants and Intrauterine Devices

ABSTRACT: Long-acting reversible contraception (LARC)—intrauterine devices and the contraceptive implant—are safe and appropriate contraceptive methods for most women and adolescents. The LARC methods are top-tier contraceptives based on effectiveness, with pregnancy rates of less than 1% per year for perfect use and typical use. These contraceptives have the highest rates of satisfaction and continuation of all reversible contraceptives. Adolescents are at high risk of unintended pregnancy and may benefit from increased access to LARC methods.

Sexual Behavior and Contraceptive Use Among American Adolescents

In the United States, 42% of adolescents aged 15–19 years have had sexual intercourse (1). Although almost all sexually active adolescents report having used some method of contraception during their lifetimes, they rarely select the most effective methods. Adolescents most commonly use contraceptive methods with relatively high typical use failure rates such as condoms, withdrawal, or oral contraceptive (OC) pills (1). Nonuse, inconsistent use, and use of methods with high typical use failure rates are reflected in the high rate of unintended adolescent pregnancies in the United States. Eighty-two percent of adolescent pregnancies are unplanned, accounting for one fifth of all unintended pregnancies in the United States, a statistic that indicates an unmet need for acceptable, reliable, and effective contraceptive methods for adolescents (2).

Long-acting reversible contraception (LARC) methods are increasing in popularity with use increasing from 2.4% of all U.S. women using contraception in 2002 to 8.5% in 2009 (3). Approximately 4.5% of women aged 15–19 years who are currently using a method of contraception use LARC, with most using an IUD (3). The etonogestrel single-rod contraceptive implant, approved by the U.S. Food and Drug Administration in 2006, is used by less than 1% of U.S. women using contraception and 0.5% of those aged 15–19 years (4).

Short-acting contraceptive methods, including condoms, OCs, the contraceptive patch, the vaginal ring, and

depot medroxyprogesterone acetate (DMPA) injections, are mainstays of adolescent contraceptive choices, but these contraceptives have lower continuation rates and higher pregnancy rates than LARC methods (5, 6). Of 1,387 females aged 15–24 years who initiated short-acting hormonal methods, only 11% using the contraceptive patch, 16% receiving DMPA injections, and approximately 30% using the vaginal ring and OCs were still using the same method after 12 months (6). In a study of 4,167 females aged 14–45 years that compared continuation rates for LARC and short-acting contraceptive methods, the continuation rate for LARC was 86% at 12 months compared with 55% for short-acting contraceptive methods (7). In this study, continuation rates for the levonorgestrel intrauterine system and the contraceptive implant in women younger than 20 years were similar to rates for older women at 85% and 80%, respectively, at 1 year. Copper IUD continuation rates were slightly lower for adolescents than for older women, but were still 72% at 1 year. In the same study population, unintended pregnancy rates for short-acting contraceptives were 22 times higher than unintended pregnancy rates for LARC. Women younger than 21 years using short-acting contraceptives had a risk of unintended pregnancy that was two times the risk among older women using short-acting contraceptives, but the risk was the same if they were using LARC (8). Poor continuation coupled with higher failure rates decrease the efficacy of short-acting contraception in young women.

Barriers to wide use of LARC methods by adolescents include a lack of familiarity with or misperceptions about the methods, the high cost, the lack of access, and health care providers' concerns about the safety of LARC use in adolescents (9–11). A large study that removed cost and other common barriers to LARC methods, and included counseling on the full range of birth control options, found that more than two thirds of females aged 14–20 years chose LARC methods (12).

Counseling, Consent, Confidentiality, and Cost

Increasing adolescent access to LARC is a clinical and public health opportunity for obstetrician–gynecologists. With top-tier effectiveness, high rates of satisfaction and continuation, and no need for daily adherence, LARC methods should be first-line recommendations for all women and adolescents (13). As with all nonbarrier methods, to decrease the risk of sexually transmitted infections (STIs), including human immunodeficiency virus (HIV), health care providers should advise sexually active adolescents to consistently use condoms along with LARC methods.

Like all women seeking reproductive health services, adolescents have the right to decline the use of LARC as well as the right to discontinue LARC without barriers. Coercive insertion of long-acting contraception was used in the past as a means of fertility control in marginalized women (14). In the absence of contraindications, patient choice should be the principal factor in prescribing one method of contraception over another, and adolescents have the right to decline any method of contraception.

Confidentiality is of particular importance to adolescents. In many states, adolescents have the right to receive confidential contraceptive services without parental consent, and health care providers should be familiar with laws concerning provision of contraception to minors in their own states. Information regarding these laws can be found at: <http://www.guttmacher.org/statecenter/adolescents.html>.

High up-front costs for LARC methods can be a deterrent to use. Adolescents who have insurance coverage through their parents may not want to use the benefit because of confidentiality concerns; others may be uninsured or have insurance that excludes coverage for LARC methods. In all of these cases, referral to a publicly funded clinic may be appropriate. Proposed health care reform provisions to cover all FDA-approved contraceptive methods, including LARC methods, without copayments or deductibles for these preventive health services, may ease this burden.

Guidance for Adolescent Health Care Providers to Address Common Misconceptions

Health care providers' concerns about LARC use by adolescents are a barrier to access. Health care provider train-

ing and continuing education programs should address common misconceptions and review the key evidence and benefits of adolescent LARC use.

Intrauterine Devices

Intrauterine devices are safe to use among adolescents.

Current evidence demonstrates the safety of modern IUDs. Although few studies have focused exclusively on adolescents who use currently available IUDs, good evidence suggests that the relative risk of pelvic inflammatory disease (PID) is increased only in the first 20 days after IUD insertion and then returns to baseline, while the absolute risk remains small (15–17). Bacterial contamination associated with the insertion process is the likely cause of infection, not the IUD itself. The risk of PID with IUD placement is 0–2% when no cervical infection is present and 0–5% when insertion occurs with an undetected infection (17). Women with positive chlamydia cultures after IUD insertion are unlikely to develop PID, even with retention of the IUD, if the infection is promptly treated (18, 19). The levonorgestrel intrauterine system may lower the risk of PID by thickening cervical mucus and thinning the endometrium (20–22).

Intrauterine devices do not increase an adolescent's risk of infertility.

Infertility is not more likely after discontinuation of IUD use than after discontinuation of other reversible methods of contraception (16). In a large case–control study that examined determinants of tubal infertility, the presence of chlamydial antibodies, not previous IUD use, was associated with infertility (23). Baseline fecundity returns rapidly after IUD removal (24).

Intrauterine devices may be inserted without technical difficulty in most adolescents and nulliparous women.

Little evidence suggests that IUD insertion is technically more difficult in adolescents compared with older women. More than one half of young nulliparous women report discomfort with IUD insertion (21). Anticipatory guidance regarding pain and provision of analgesia during IUD insertion should be individualized and may include supportive care, nonsteroidal antiinflammatory drugs (NSAIDs), narcotics, anxiolytics, or paracervical blocks. The most effective method of pain control has not yet been established (25). Use of buccal or vaginal misoprostol 2–3 hours before IUD insertion to soften a nulliparous cervix does not appear to reduce insertion pain, and adverse effects are common (26–28).

Adolescents should be routinely screened for STIs (eg, gonorrhea and chlamydia) at the time of IUD insertion.

Women aged 15–19 years have the second highest rates of chlamydia and the highest rates of gonorrhea of any age group (29). Thus, all adolescents should be screened for STIs at the time of or before IUD insertion. It is reasonable to screen for STIs and place the IUD on the same day (and administer treatment if the test results are positive)

or when the test results are available. If an STI is diagnosed after the IUD is in place, it may be treated without removing the IUD (30–32). Routine antibiotic prophylaxis is not recommended before IUD insertion (33).

Intrauterine device expulsion is uncommon in adolescents.

Intrauterine device expulsion rates range from 3% to 5% for all IUD users and from 5% to 22% in adolescents (34, 35). Young age, previous IUD expulsion, and nulliparity may slightly increase the risk of expulsion, but research on current IUDs is limited (34–36). Prior expulsion should not be considered a contraindication for another IUD provided that appropriate counseling is given (36).

Intrauterine devices cause changes in bleeding patterns.

Adolescents using either copper IUDs or the levonorgestrel intrauterine system can expect changes in their menstrual bleeding especially in the first months of use. The copper IUD may cause heavier menses that can be treated with NSAIDs. Women using the levonorgestrel intrauterine system will have a decrease in bleeding over time that will lead to light bleeding, spotting, or amenorrhea. Health care providers should counsel adolescents so they understand that these changes are expected.

The Contraceptive Implant

The contraceptive implant causes changes in bleeding patterns.

Adolescents who use the contraceptive implant can expect changes in menstrual bleeding patterns throughout the duration of use. In an analysis of 11 clinical trials, including 942 etonogestrel implant users of all ages, the most common bleeding pattern was infrequent bleeding in 33.3% of 90-day cycles, followed by amenorrhea in 21.4% of cycles. Prolonged bleeding occurred in 16.9% of cycles and frequent bleeding occurred in 6.1% of cycles (37). A change in bleeding pattern is the most common reason for implant discontinuation. Anticipatory guidance regarding bleeding patterns may improve satisfaction and continuation. The bleeding pattern women experience in the first 3 months is broadly predictive of future bleeding patterns (38).

Common strategies for treating problematic bleeding include the use of short courses of combined OCs or NSAIDs; however, there are no published placebo controlled trials to support the use of these treatments (39). Limited clinical trial data suggest that, compared with placebo, mefenamic acid, mifepristone in combination with ethinyl estradiol or doxycycline, and doxycycline alone decrease the length of bleeding episodes in implant users (40–42). More research is needed to determine whether these or other interventions affect long-term continuation or acceptability of the implant.

The contraceptive implant has secondary health benefits.

High rates of infrequent bleeding or amenorrhea lead to higher hemoglobin levels in etonogestrel implant users

(43). Other noncontraceptive benefits of the contraceptive implant include reductions in dysmenorrhea and pelvic pain (44, 45). A prospective study of etonogestrel implant users showed no difference in the change in bone mineral density compared with copper IUD users after 2 years of use (46).

The contraceptive implant has minimal or no effect on weight.

Currently, no prospective studies of weight in etonogestrel implant users have been published. A small percentage of women (2.3%) in the clinical trials for the etonogestrel implant discontinued use because of reported weight gain; however, actual weight gain was not documented (37). In contrast, DMPA injections are associated with weight gain, with overweight adolescents more susceptible to weight gain than normal weight adolescents (47).

Postpartum and Postabortal Long-Acting Reversible Contraception Initiation

Postpartum Long-Acting Reversible Contraception

Adolescent mothers are at high risk of rapid repeat pregnancy; 20% give birth again within 2 years (48). Insertion of an IUD or implant immediately postpartum ensures reliable contraception for adolescents when they are highly motivated to prevent pregnancy and are already in the health care system. The benefits of postpartum IUD insertion outweigh the risks, although recommendations vary depending on the type of device and timing of postpartum insertion (see Table 1) (31). Although the risk of expulsion is higher for immediate insertion compared with delayed insertion, if a delayed insertion presents a significant barrier, immediate insertion should be offered (49). Of adolescents in the postpartum period who received care from a clinic that prioritizes contraceptive use, the implant was more likely to be placed before resumption of sexual activity than the IUD, thus reducing repeat pregnancy (50).

Postabortal Long-Acting Reversible Contraception

Almost one half of all abortions performed in the United States are repeat abortions (51). Inserting an IUD or implant immediately after abortion significantly reduces the risk of repeat abortion (52). As is the case with older women, the benefits of providing LARC to adolescents after a spontaneous or induced abortion outweigh the risks (see Table 1). The implant is safe to place after any abortion, including second-trimester or septic abortion (31). Intrauterine devices are safe to place after a first-trimester or second-trimester abortion; however, the adolescent should be counseled about the possibility of IUD expulsion. Data on postabortal etonogestrel implant

Table 1. U.S. Medical Eligibility Criteria for Contraceptive Use

Condition	Implant	Copper IUD	LNG-IUD	Clarification/Evidence/Comments
Age				
Menarche to younger than 18 y	1			
Menarche to younger than 20 y	1	2	2	Comment: Concern exists about the risk for expulsion from nulliparity and for STIs from sexual behavior in younger age groups.
Postpartum				
Less than 10 min after delivery of the placenta		1	2	Evidence: Immediate postpartum insertion of a copper IUD, particularly when insertion occurs immediately after delivery of the placenta, is associated with lower expulsion rates. Immediate insertion may happen after vaginal or cesarean birth.
10 min after delivery of the placenta to less than 4 wk	2	2	2	
Less than 4 wk and not breastfeeding	1	2	2	
Less than 4 wk and breastfeeding	2	2	2	
4 wk or later and breastfeeding or not breastfeeding	1	1	1	
Puerperal sepsis		4	4	Comment: Insertion of an IUD might substantially worsen the condition.
Postabortion				
				Evidence: Risk for complications from immediate insertion versus delayed insertion of an IUD after abortion did not differ. Expulsion was greater when an IUD was inserted after a second-trimester abortion than when inserted after a first-trimester abortion. Safety and expulsion for postabortion insertion of an LNG-IUD did not differ from that of a copper IUD.
First trimester	1	1	1	Clarification: IUDs can be inserted immediately after first-trimester spontaneous or induced abortion.
Second trimester	1	2	2	
Immediately after septic abortion	1	4	4	Comment: Insertion of an IUD might substantially worsen the condition.

1 = A condition for which there is no restriction for the use of the contraceptive method.
2 = A condition for which the advantages of using the method generally outweigh the theoretical or proven risks.
3 = A condition for which the theoretical or proven risks usually outweigh the advantages of using the method.
4 = A condition that represents an unacceptable health risk if the contraceptive method is used.
Abbreviations: IUD, intrauterine device; LNG-IUD, levonorgestrel-releasing intrauterine device.
Modified from U.S. Medical Eligibility Criteria for Contraceptive Use, 2010. Centers for Disease Control and Prevention (CDC). MMWR Recomm Rep 2010;59(RR-4):1–86.

safety and repeat abortion are lacking but can be extrapolated from data on IUDs and previous experience with a six-rod implant system that is no longer marketed in the United States that shows these methods were easy and safe to use and highly effective (53, 54).

Conclusion

When choosing contraceptive methods, adolescents should be encouraged to consider LARC methods. Intrauterine devices and the contraceptive implant are

the best reversible methods for preventing unintended pregnancy, rapid repeat pregnancy, and abortion in young women. Counseling about LARC methods should occur at all health care provider visits with sexually active adolescents, including preventive health, abortion, prenatal, and postpartum visits. Complications of IUDs and the contraceptive implant are rare and differ little between adolescents and older women. Health care providers should consider LARC methods for adolescents and help make these methods accessible to them.

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Parte I

Aspectos generales, normativos e históricos

1.

**Salud sexual y reproductiva integral,
conceptos, legislación y prioridades**

En nuestra cultura, con frecuencia la sexualidad va ligada directamente a la vida reproductiva de la mujer, quedando relegada a ser una situación placentera al servicio de la procreación. Por otra parte, el papel sexual se puede considerar como una categorización social de las conductas en nuestra sociedad, deseables para un individuo, pero no para otro; es decir que una conducta según el sexo de quien lo lleva a cabo refleja lo esperado o inesperado. En nuestras culturas latinoamericanas por lo general cuando nace un ser humano y se identifica su sexo, la sociedad enfoca sus expectativas y el niño o la niña recibe permanentemente la influencia del entorno que lo o la rodea y empiezan los regalos azules o rosados según el sexo, el tipo de vestidos son diferentes y se comienza a diferenciar e influenciar las posibilidades de expresión. Si el niño llora, se intenta callarlo con expresiones como "los hombres no lloran"; si es niña, se asume que debe protegerse, pues "es débil y delicada", y que "finalmente la mujer viene al mundo a sufrir".

Si la niña se tropieza y cae, se le alzarán de forma protectora y se colmará de cuidados; si es un varón, se le incita a levantarse, a no llorar y sobreponerse para continuar.

Es entonces en el entorno familiar especialmente donde el rol sexual se establece mediante la imitación e imposición, reforzando las necesidades creadas en el niño o la niña de adoptar un género e incorporarlo a su personalidad, lo cual se verá reflejado en un comportamiento social, masculino o femenino, que dependerá de los estereotipos sociales según el estrato sociocultural. Lo anterior se ve reforzado en la vida cotidiana, en los planteles educativos y se va estableciendo arbitrariamente un abanico de posibilidades para uno y otro género teniendo como base una supuesta debilidad en la mujer y una mayor fuerza en el hombre.

¿Hay razones biológicas para suponer un papel pasivo de la mujer y uno activo del hombre? Lo activo y lo pasivo carecen de una determinación biológica universal y atemporal en relación con el sexo.

Lamentablemente en nuestro mundo machista la situación de la mujer es de vulnerabilidad; es por eso que dos terceras partes del analfabetismo mundial recae en las mujeres, muere más de una mujer cada minuto como

extractos de la *Lonicera peryclaymenum*, que durante 36 días podría producir esterilidad masculina.

Aristóteles (421 a.C.) describía el uso del poleo como un anticonceptivo e Hipócrates (460-377 a.C.) sostenía que la semilla de la zanahoria salvaje podía impedir el embarazo.

En Grecia, Sorano (98-138 d. C.), escribió un tratado sobre anticoncepción que estuvo vigente hasta el siglo XIX.

El uso de la anticoncepción se diseminó en Europa a través del islam, ya que sus leyes no condenaban el aborto en esa época, realizado antes de los cuatro meses por razones "serias", ni el control de la natalidad. Por ende, los métodos anticonceptivos se transmitían por tradición de unos a otros, por las parteras e incluso médicos islámicos, quienes hicieron tratados sobre el tema. Es así como Rhazes (850-923) y Avicena de Hamadan (980-1037) aceptaban la anticoncepción como parte integral de la práctica médica y detallaron métodos como oclusión vaginal, ungüentos y el AZL (coito interrumpido), este último muy mencionado en las primeras enseñanzas mahometanas.

Santo Tomás de Aquino (1225-1274) condenó la práctica médica de la anticoncepción y esta prohibición se convirtió en parte integral de la doctrina católica, posición reafirmada por Pablo VI en su encíclica de 1968 (*Humanae Vitae*), donde declara que los actos del matrimonio deben permanecer abiertos a la transmisión de la vida. Esta posición ha sido la constante hasta nuestros días, de tal forma que la Iglesia católica solo acepta la planificación familiar natural.

Los primeros condones se remontan a la época de los romanos, que los fabricaban de vejigas o intestinos de animales. En 1564, Falopio describió una funda de lino para prevenir la lúes, pero solo hasta 1843, con la vulcanización del caucho, se dio paso al desarrollo comercial del condón.

La idea del dispositivo intrauterino es muy antigua, atribuyéndose a Hipócrates la introducción de elementos extraños intrauterinos utilizando un tubo de plomo para tal fin. Existe la leyenda de que los primitivos nómadas colocaban piedras dentro del útero de las camellas para evitar dificultades en los viajes. En 1909, el alemán Richter usó un dispositivo intrauterino (DIU), que consistía en una cuerda hecha con tripa de gusano de seda. En 1916, Robert Dickinson utilizó tallos intrauterinos como método anticonceptivo. En 1929, Gräfenberg describió un anillo de metal cuyo uso se discontinuó por las lesiones cervicales que se producían al colocarlo y retirarlo. Posteriormente, el uso de materiales modernos flexibles permitió nuevamente su uso. En 1934, Ishihama y Ota en Japón e Israel, respectivamente, emplearon por primera vez material plástico. En 1959, Margulies en Nueva York, presenta el primer dispositivo asociado a bario, y en 1960, Lippes, en la Universidad de Buffalo, desarrolla un nuevo DIU en forma de doble "S" (Asa de Lippes). En 1963, Jaime Zipper, luego de experiencias en conejas con el DIU de polietileno y

bario en forma de "T", ideado por Tatum, decide agregarle cobre con el fin de obtener mayor efectividad y así se inicia la era de la segunda generación de dispositivos, los llamados bioactivos.

Los peligros que representa para la sociedad el ilimitado aumento de la población fue vagamente reconocido por escritores antiguos, hasta que el clérigo y economista inglés Thomas Malthus hizo la primera formulación clara del problema en su obra: "Un ensayo sobre el principio de población y cómo afecta el futuro mejoramiento de la sociedad".

Historia de la anticoncepción hormonal

Brevemente resumiremos los aspectos más relevantes de la historia de la anticoncepción hormonal. En 1600, De Graff describió los folículos ováricos, y Emil Knauer, en Viena, atribuía a las hormonas ováricas la aparición de las características sexuales femeninas. En 1897, Beard sugirió que la ovulación se inhibía durante el embarazo por efecto del cuerpo amarillo. En 1921, Haberlandt, al trasplantar ovarios de animales gestantes a hembras sexualmente maduras, produjo infertilidad, vislumbrando la inhibición de la ovulación como algo posible. En 1933, Hartman sugirió a un colega que utilizara un preparado de estrógenos de líquido amniótico bovino como anticonceptivo.

En 1928, George Corner y William Allen denominaron progesterona a la hormona que facilitaba la implantación del embarazo. Posteriormente, en 1929, Eduard Doisy identificó la hormona que inicialmente había estudiado Knauer y la llamó estrógeno (*oistros* = deseos locos, *gennein* = engendrar).

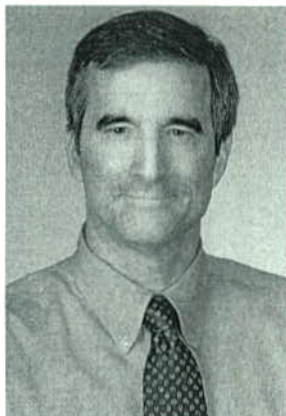
En 1932, Edward Doisy (premio Nobel en 1943) procesó 80.000 ovarios de cerda para obtener 12 mg de Estradiol, y necesitó los ovarios de 2.500 cerdas embarazadas para obtener 1 mg de progesterona. Ya en 1938 se sintetiza el etinil-estradiol; en 1940, Sturgis y Albright, al emplear estrógenos inyectados, no solo inhibían la ovulación, sino que mejoraban la dismenorrea. Para 1944, Russell Marker obtiene progesterona a partir de diosgenina (raíz de la planta "Cabeza de negro"). Posteriormente se encontró que en la raíz del barbasco había diez veces más cantidad de diosgenina. Para esa época, Syntesis y G.D. Searle anunciaron la elaboración de dos derivados de la progesterona: la Noretindrona y el Noretinodrel, que serían los gestágenos de los primeros anovulatorios orales.

En 1951, la Worcester Foundation for Experimental Biology patrocina el trabajo de John Rock en Harvard, Gregory Pincus y Chang en Worcester. Por la misma época, Carl Djerassi sintetiza el 17-alfa etinil 19-nortestosterona que tenía una actividad diez veces mayor que la progesterona.

Para 1956, en Puerto Rico y Haití se inicia el uso de los anovulatorios orales combinados con el Enovid* (0,15 mg de 9,85 Mestranol y 9,85 mg de Noretindrona), y la primera píldora de solo progestina Norlutin* (Noretindrona).

The Intrauterine Device

A Good Thing Revisited



David E. Soper, MD

See related articles on page 934, 943 and 1091.

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Over the past decade, intrauterine device (IUD) use by women in the United States has increased from 1.3% of total contraceptive use in 2002 to 8.5% in 2007–2009.¹ Although this increase still does not exceed the nearly 10% rate seen in the 1970s, it does suggest an improving comfort level by physicians and patients alike in choosing this type of long-acting reversible contraception. A better understanding of the reasons behind early discontinuation, the development of new therapeutic uses, and a better appreciation of the low risk of adverse outcomes associated with the IUD has spurred interest in this option not only for contraception but also for therapeutic intervention.² In this issue of *Obstetrics & Gynecology*, we note investigators addressing all three issues regarding the modern use of the levonorgestrel-releasing intrauterine system (see pages 934, 943, and 1091).^{3–5}

Sordal et al (see p. 934)³ address one of the more common unintended consequences of levonorgestrel-releasing intrauterine system insertion. Up to two thirds of women receiving the levonorgestrel-releasing intrauterine system report irregular bleeding after placement, which significantly declines to less than 20% of those choosing to continue using the device through the first year. With counseling, most women experiencing levonorgestrel-releasing intrauterine system metrorrhagia will not discontinue the device. However, clinicians and their patients would welcome a reliable intervention to minimize the inconvenience of this menstrual irregularity. To that end, the investigators compared two plausible medical therapies, tranexamic acid (an anti-fibrinolytic) and mefenamic acid (a nonsteroidal anti-inflammatory agent), with placebo. The cumulative number of bleeding or spotting days during the 90-day treatment period after insertion was counted. Women bled or spotted for 25 to 33 days out of the 90 days after insertion, and no clinically meaningful differences were noted among the study groups. Despite the absence of therapeutic benefit, women were satisfied (continuation rates of more than 96%) with the levonorgestrel-releasing intrauterine system, even in the short term. Given that placebo was as effective as the medical interventions, we can conclude that these medications need not be prescribed for this common side effect of intrauterine system insertion.

The noncontraceptive benefits of the levonorgestrel-releasing intrauterine system are numerous. Reports show its efficacy in the therapy of heavy menstrual bleeding, in the treatment of endometrial hyperplasia and adenocarcinoma in poor surgical candidates, and as a progestin source for women using estrogen therapy.^{2,6,7} Wong et al (see p. 943)⁴ have completed their 5-year follow-up study using the levonorgestrel-releasing intrauterine system for the prevention of tamoxifen-associated endometrial polyps. Women with breast cancer on tamoxifen were randomized to levonorgestrel-releasing intrauterine system insertion or control group and underwent hysteroscopy at baseline, 12 months, 24 months, 45 months, and 60 months. The report confirms their preliminary



observations published after 1 year of follow-up, in that the levonorgestrel-releasing intrauterine system was effective in preventing endometrial polyps in the treatment group. However, it is noteworthy that these were small, asymptomatic endometrial polyps and arguably not worth the effort to actively pursue in the first place. They were not able to determine whether the levonorgestrel-releasing intrauterine system also would prevent endometrial hyperplasia and cancer in these patients, but no increased risk of breast cancer recurrence was noted.

We are reminded by Hubacher et al (see p. 1091)⁵ of the rejection of the IUD in the United States in the 1980s and 1990s owing to its association with infection.⁸ Thankfully, ongoing research has resulted in better devices—the copper IUD and the levonorgestrel-releasing intrauterine system—and further study has clarified the risk of infection as being rare and related to the presence of sexually transmitted infection and not the IUD.^{9,10} The authors methodically take us through the difficulties in studying pelvic inflammatory disease (PID), with its imprecise diagnosis and the methodologic flaws that make investigation of the IUD–PID relationship fraught with pitfalls. Although determining the adverse outcomes associated with IUD use is important, accurate reporting is paramount because conclusions based on erroneous information could destroy what has become an important option for the prevention of unintended pregnancy, especially in adolescents.

The use of the intrauterine device is alive and well these days, as it should be. Continued efforts to fine-tune these devices by minimizing their nuisance side effects and developing valuable new indications will be a good thing for women in the 21st century.

Careful study of potential adverse outcomes remains important.

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Original Article

A study investigating obstetricians' and gynaecologists' management of women requesting an intrauterine device

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Background: Intrauterine methods including the copper intrauterine device (Cu-IUD) and the levonorgestrel intrauterine system (LNG-IUS) provide highly effective long-term reversible contraception. The reasons for relative low use of these methods in Australia compared to many European countries are not clear, but may in part relate to provider reluctance because of outdated knowledge about their safety and efficacy.

Aims: The aim of this study was to survey Australian Fellows of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists about their knowledge of the risks, benefits and mechanisms of action of intrauterine methods.

Methods: In 2008, we undertook a cross-sectional survey of all Australian Fellows not registered as a subspecialist. The survey was mailed to 1050 practitioners and 701 were returned, comprising a response rate of 67%.

Results: Knowledge about the LNG-IUS was significantly better than for the Cu-IUD in terms of correct understanding about mechanism of action (89.3% vs. 30%; $P < 0.001$) and efficacy (63.2% vs. 33.5%; $P < 0.001$). According to the WHO, both methods are considered suitable for use in nulliparous women, yet only 39.1% of providers believed the Cu-IUD suitable compared to 69.4% for the LNG-IUS ($P < 0.001$). When responses were analysed according to time from graduation, many aspects of knowledge about these devices showed a linear trend, with greater accuracy in recent graduates (<10 years) compared with graduates of more than 30 years.

Conclusion: Both methods are highly effective, non-user dependent and reversible and deserve greater understanding and consideration for use by Australian practitioners and women.

Key words: intrauterine device, knowledge, levonorgestrel intrauterine system.

Introduction

Intrauterine contraceptive devices (IUDs), including the copper intrauterine device (Cu-IUD-Multiload, Shering Plough and Copper T380, Medical Industries of Australia) and the levonorgestrel intrauterine system (LNG-IUS; Mirena, Bayer Schering Pharma, Australia) are highly effective methods that have failure rates, which are similar to, or better than, sterilisation.¹ IUD methods are rapidly reversible and will not impact on subsequent fertility unless a woman experiences acute pelvic inflammation around the time of insertion believed to be related to the presence of an underlying, unrecognised sexually transmitted infection (STI).² IUDs are therefore not contraindicated in uninfected nulliparous women.³

Importantly, the risk of pelvic infection seems to be confined to the first 20 days after insertion and, in low-risk populations, this is very uncommon.⁴ Both the Cu-IUD and the LNG-IUS have a pre-fertilisation mechanism of action: the Cu-IUD through copper ions having a toxic effect on spermatozoa and the LNG-IUS primarily through progestogen action on cervical mucous and the endometrium.⁵ The copper IUD can also be used for emergency contraception up to five days after unprotected sex and is more effective than oral emergency contraceptive pills in preventing pregnancy.⁶

During the last five years, the growth in popularity of the LNG-IUS has re-ignited interest in intrauterine methods. Nevertheless, in Australia, they remain a relatively uncommon contraceptive choice, with published data from 2002 suggesting that only 2% of women were using them. However, with increased uptake of the LNG-IUS, the figure is likely to be around 5% in 2009.^{7,8} In contrast, 7% of British women⁹ and 23% of women in Norway¹⁰ rely on IUDs for contraception. The reasons for these differences are not known, but it is likely that reluctance to use the methods may result from a lack of understanding of recent evidence.⁴ The 1970s class actions against the manufacturers

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of the Dalkon Shield IUD in the USA, which also involved Australian women, linked that particular device to pelvic infection, infertility and even death from sepsis. There is good evidence that modern devices do not carry the same risks, but unbalanced information about the benefits and risks of using IUDs persist and result in practitioner reluctance to recommend these methods.¹¹⁻¹⁴

There is a growing consensus in the international family planning community that a focus on long-acting methods (including IUDs), which are less user-dependent and therefore more reliable, may be the most effective strategy in reducing rates of unplanned pregnancies.¹⁵ It is thus valuable that Australian obstetricians and gynaecologists have up-to-date knowledge and understanding of IUDs and their use, both as a form of emergency contraception (in the case of Cu-IUDs) as well as their use as very reliable long-acting contraceptive methods. The primary objective of this study was to investigate the clinical practices of Australian Fellows of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) managing women requesting an IUD; to survey their knowledge of the risks, benefits and mechanisms of action of these methods.

Methods

Between January and June 2008, we undertook a cross-sectional survey of Australian RANZCOG Fellows of their

knowledge and clinical practices in managing women requesting a Cu-IUD or an LNG-IUS (Mirena®). The questionnaire was sent with a reply paid envelope to all 1050 Fellows not registered as subspecialists. Non-responders at eight weeks were mailed a repeat questionnaire with a reply paid envelope and a modified letter of introduction.

The questionnaire was designed by a gynaecologist (KB) and a clinical microbiologist who is also a sexual health physician (SMG). The questions were structured with five possible responses. When asking a clinician about their knowledge, the response options were 'strongly agree', 'agree', 'uncertain', 'disagree' and 'strongly disagree' and for the purposes of analysis the responses 'agree' and 'strongly disagree' were grouped together. When asking clinicians about aspects of their clinical practice, the response options were 'always', 'usually', 'sometimes', 'rarely' or 'never'. The key questions along with the responses considered correct and the evidence behind these are documented in Table 1.

Prior to mailing, the questionnaire was piloted with ten gynaecologists and reviewed by the Continuing Professional Development Committee of RANZCOG. This led to several modifications in the wording and content of the questionnaire.

The study was undertaken through the Royal Women's Hospital in Melbourne, and the Department of Obstetrics and Gynaecology at the University of Sydney and approved by the Ethics Committee of the Royal Women's Hospital

Table 1 Questionnaire content and correct responses as guided by the Faculty of Sexual & Reproductive Health Care of the Royal College of Obstetricians and Gynaecologists^{16,18}

Statement	Correct response	Reason
The primary mode of action of Cu-IUDs is to prevent the sperm fertilising the egg	Strongly agree or agree	Copper is toxic to sperm so the devices work primarily by inhibiting fertilisation
The primary mode of action of the LNG-IUS is inhibition of ovulation	Disagree or strongly disagree	The LNG-IUS works through the effect of levonorgestrel on the endometrium and cervical mucous
The LNG-IUS has a failure rate similar to sterilisation	Strongly agree or agree	The failure rate of IUDs is similar to sterilisation
The Cu-IUD has a failure rate similar to sterilisation	Strongly agree or agree	The failure rate of the LNG-IUS is similar to sterilisation
Previous use of a Cu-IUD will adversely affect fertility	Disagree or strongly disagree	There is no evidence for an adverse effect on fertility
Previous use of a LNG-IUS will adversely affect fertility	Disagree or strongly disagree	There is no evidence for an adverse effect on fertility
The Cu-IUD is suitable for use in nulliparous women	Strongly agree or agree	The WHO medical eligibility criteria for contraceptive use class nulliparity as Category 2 (benefits outweigh the risks)
The LNG-IUS is suitable for use in nulliparous women	Strongly agree or agree	The WHO medical eligibility criteria for contraceptive use class nulliparity as Category 2 (benefits outweigh the risks)
The Cu-IUD can be used as emergency contraception up to five days after an episode of UPSI	Strongly agree or agree	The Cu-IUD is very effective for use as emergency contraception
The Cu-IUD is a more reliable form of emergency contraception compared to oral levonorgestrel	Strongly agree or agree	The Cu-IUD is 99% effective compared to oral levonorgestrel which is 84% effective
The LNG-IUS can be inserted for emergency contraception	Disagree or strongly disagree	There is no evidence for the use of LNG-IUS for emergency contraception

Cu-IUD, copper intrauterine device; LNG-IUS, levonorgestrel intrauterine system.

who considered that it did not require formal ethics approval being an audit of current clinical practice. We entered responses to the questionnaire into a purpose built database and all analyses were undertaken in spss version 16.0 (Chicago, IL, USA) with chi-squared tests used to compare the matching responses for the two types of intrauterine devices. We investigated the association between knowledge and years from graduation using chi-square linear by linear association.

Results

Of 1050 Australian Fellows we surveyed, 723 questionnaires were returned. Of these, 20 were blank and two were duplicated. The results are thus based on 701, a 67% response rate. Missing data were present for 2–4% of each response reported below. More than 15% (107) of the responders were practising only in the public sector and about 26% (181) practised only in private. More than 58% (401) of the practitioners were practising in both public and private institutions. Just over half (51%; *n* = 348) of Fellows responding to the survey inserted <5 IUDs per month. Another 38% (263) reported inserting between five and ten and only 10.6% inserted more than ten a month.

Indication for use

When asked about the suitability of intrauterine devices in nulliparous women, most practitioners stated that the LNG-IUS was a suitable option, but that a Cu-IUD was not (69.4% vs. 39.1%) (Table 2). More than two-thirds (70.1%; 485) of the practitioners affirmed that a Cu-IUD could be used for emergency contraception within five days of unprotected intercourse, but only one quarter (26.0%; 179) considered it to be a more reliable option than oral emergency contraception. Forty-seven per cent (325) of respondents believed an LNG-IUS could be used for emergency contraception.

Mechanism of action

Practitioners correctly responded to statements about the mechanism of action in 30% of cases (206) for Cu-IUD and in 89.3% of cases (616) regarding the LNG-IUS (Table 2). Participants were significantly more likely to agree that the failure rate was comparable to sterilisation in relation to the LNG-IUS compared to the Cu-IUD (63.2% vs. 33.5%; *P* = 0.001).

Previous sexually transmitted infections, screening and treatment of infections

A past history of an STI was considered a contraindication to a Cu-IUD by 59.7% (412) of those responding. A greater proportion of practitioners reported that they always or usually screened women for chlamydia prior to Cu-IUD (34.8%, 236) insertion compared to LNG-IUS insertion (28.5%; 194) (*P* < 0.001). A significantly greater proportion of practitioners also reported screening for bacterial vaginosis prior to Cu-IUD compared with LNG-IUS (26.8% vs. 22.6%; *P* = 0.001).

In women with a Cu-IUD or an LNG-IUS *in situ* who test positive to *Chlamydia trachomatis* infection without symptoms and signs of infection, 37.7% (247) of participants stated that they would always or usually leave the device *in situ* whilst treating the infection. In the presence of symptoms of pelvic infection, 97.3% (653) said that they would remove it. The presence of actinomyces-like organisms on a Pap smear was considered a reason to always or usually remove the Cu-IUD or LNG-IUS, even in the absence of symptoms or signs of pelvic infection by 49.5% (335) and in the presence of symptoms or signs of infection by 92.1% (628).

Knowledge and time from graduation

Analysis of the responses in relation to years from graduation revealed that accurate knowledge about the Cu-IUD and LNG-IUS mechanism of action, failure rate of devices, reasons for failure and impact on fertility rate was for all but two questions greatest in those practitioners who had obtained their fellowship within the last ten years. The key findings are presented in Table 3 and demonstrate the linear trend of years from graduation when compared to accurate responses.

Discussion

This study documented the knowledge and practices of Australian obstetricians and gynaecologists around managing women requesting an intrauterine device and demonstrated that, in key areas, understanding of the risks and benefits of these methods is lagging behind current evidence. A significant difference in the knowledge of the participants according to the time since graduation was apparent, with more recent graduates having more up-to-date knowledge about most aspects of both Cu-IUD and LNG-IUS.

Table 2 Responses comparing Fellows' knowledge of Cu-IUDs and LNG-IUS

Knowledge areas	Cu-IUD % (<i>n</i>)	LNG-IUS % (<i>n</i>)	<i>P</i> -value
Mechanism of action correctly understood	30 (206)	89.3 (616)	<0.010
Failure rates correctly known	33.5 (232)	63.2 (438)	<0.001
Use of device will have an adverse effect on fertility	5.6 (38)	3.4 (23)	<0.001
Suitability of device in nulliparous women	39.1 (269)	69.4 (476)	<0.001

Cu-IUD, copper intrauterine device; LNG-IUS, levonorgestrel intrauterine system.

Table 3 Knowledge and time from RANZCOG Fellowship

Years from obtaining RANZCOG Fellowship	<10 years (n)	10–20 years (n)	20–30 years (n)	>30 years (n)	P-value*
Understand that the most likely reason for Cu-IUD failure is expulsion	60.4 (145)	42.7 (73)	38.8 (64)	59.1 (55)	<0.001
Believe that previous use of Cu-IUD will adversely affect fertility	2.9 (7)	6.5 (11)	6.0 (10)	10.9 (10)	0.009
Agree that Cu-IUD suitable for use in nulliparous women	43.6 (106)	39.8 (68)	30.4 (51)	39.4 (37)	0.067
Agree that Cu-IUD can be used for emergency contraception	81.3 (196)	76.0 (130)	58.3 (98)	49.5 (46)	<0.001
Agree that the LNG-IUS is a suitable option in nulliparous women	79.3 (191)	69.4 (118)	62.9 (107)	57.9 (55)	<0.001
Agree that the primary mode of action of LNG-IUS is inhibition of ovulation	7.9 (19)	7.1 (12)	7.6 (13)	20.0 (19)	0.010
Agree that LNG-IUS has a failure rate similar to sterilisation	61.8 (149)	67.1 (114)	64.7 (110)	54.7 (52)	0.464
Believe that previous use of LNG-IUS will adversely affect fertility	1.6 (4)	3.6 (6)	3.5 (6)	8.7 (8)	0.006

*Linear trend.

Cu-IUD, copper intrauterine device; LNG-IUS, levonorgestrel intrauterine system; RANZCOG, Royal Australian and New Zealand College of Obstetricians and Gynaecologists.

There was a lack of up-to-date information regarding the Cu-IUD around knowledge of mechanism of action, reliability of the device and use as a method of emergency contraception. Although both national and international guidelines do not regard nulliparity as a contraindication to Cu-IUD or LNG-IUS use, more than half (54.6%) of the responders considered the Cu-IUD not suitable in this group.³ While most of the Fellows were aware that Cu-IUD could be used as emergency contraception, only one quarter (26.1%) were aware that it is a more reliable option than oral emergency contraception.

Knowledge about the LNG-IUS was significantly better in all respects. There was some confusion about the use of the LNG-IUS for emergency contraception, with almost half believing (incorrectly) that it was a suitable option. Most practitioners responded correctly to questions about efficacy, mechanism of action and impact on subsequent fertility. Two-thirds of responders recognised that the LNG-IUS is as effective as sterilisation.

Many practitioners (59.7%) responding to the questionnaire believed that a Cu-IUD could not be used in women with a past history of an STI. Although the presence of an STI or pelvic inflammatory disease (PID) at the time of insertion is a contraindication, a past history of an STI, particularly with appropriate treatment is not.³ International and local guidelines indicate that screening for chlamydia is recommended for women considered at risk of an infection, but that routine screening is not required. Screening for bacterial vaginosis in asymptomatic women is not recommended, but should it be inadvertently found, treatment is recommended prior to IUD insertion.^{16,17}

The latest guidelines from the WHO and from the Faculty of Sexual and Reproductive Healthcare in the United Kingdom do not routinely recommend the removal of the IUD in women who develop an STI infection or PID, but rather suggest treatment with the device *in situ* provided there is a good response.^{3,18} This guidance differs from advice from the British Association for Sexual Health and HIV (BASHH), which states that removal of the IUD should be considered. Their guidance is based on evidence from a randomised study in which women with clinically

mild or moderate PID had better short-term outcomes when the treatment followed IUD removal.^{19,20} This is the approach supported by sexual health physicians and clinical microbiologists, including one of the authors (SMG).

Several developments have re-focussed attention on intrauterine devices. The growth in popularity of the LNG-IUS has led to renewed acceptance of these methods and the results from this study show that specialist obstetricians and gynaecologists perceive the LNG-IUS to be safer and more reliable. The IUS significantly reduces menstrual bleeding and there is some evidence of its effectiveness in managing the symptoms of adenomyosis and endometriosis.^{21,22} The copper devices have the advantage of being hormone-free so are a good option for women in whom exogenous hormones are contraindicated. There is also sound evidence of a reduction in endometrial cancer with either long-term Cu-IUD or LNG-IUS use.²² Both methods are highly effective, non-user-dependent and reversible and deserve greater understanding and consideration for use by Australian practitioners and women.

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Comparison of levonorgestrel and copper releasing intrauterine contraceptive device on body iron stores and menstrual bleeding patterns: experience on Indian women

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Abstract. – Introduction: The search for an ideal contraceptive device most suited for women of developing countries with anemia poses a challenge.

Aim: This study was conducted to compare the effects of levonorgestrel releasing (LNG) and copper releasing (Cu T) intrauterine contraceptive devices (IUCD) on body iron stores and menstrual bleeding patterns.

Methods: Hundred women desiring contraception were divided into two groups of fifty each where either LNG or Cu T 200 IUCD was inserted. Outcome parameters evaluated were change in menstrual bleeding patterns, serum ferritin and hemoglobin level post insertion at three, six and twelve months. Main outcome measures were change in serum ferritin, hemoglobin concentration, menstrual bleeding and spotting days 12 months after insertion.

Results: Menstrual bleeding days increased initially at three month for both IUCD's, but by 12 months, mean number of bleeding days reduced from preinsertion 4.96 ± 1.61 to 3.14 ± 1.72 days ($p < 0.05$) in the LNG group while in Cu T number of bleeding days remained higher at 12 months (4.76 ± 0.96 days) compared to pre-insertion level (4.46 ± 0.91 days, $p = \text{NS}$). At 12 months, 60% women developed hypomenorrhea and 20% had amenorrhea in LNG group. Higher ($p < 0.05$) serum ferritin (24.17 ± 5.97 vs. 20.80 ± 5.78) and hemoglobin (12.45 ± 0.46 vs. 11.95 ± 11.042 gm/dl) concentration was noted in the LNG group as compared to Cu T by the end of 1 year.

Conclusion: LNG reduced the number of menstrual bleeding days and increased the hemoglobin and serum ferritin levels, thus preventing loss of body iron. This may be especially important for women in developing countries like India where decrease in blood loss may improve iron deficient situations.

Key Words:

Levonorgestrel, Cu T, Serum ferritin, Hemoglobin, Bleeding patterns.

Introduction

Intrauterine contraceptive device (IUCD) is an effective and convenient contraceptive method which has failed to gain adequate acceptance because the presently available inert and copper releasing intrauterine devices increase the menstrual blood loss sometimes to such an extent as to cause iron deficiency anemia^{1,2}. In developed countries women with adequate nutrition may make up for this blood loss but those with higher prevalence of anemia are at serious health risks due to the increased blood loss.

The recognition of the favorable effect of oral steroid contraception on the amount of menstrual blood loss has been part of the basis for development of a steroid releasing intrauterine device. Levonorgestrel intrauterine system (LNG), Mirena® (Schering Pharmaceuticals, Hong Kong, China) is a T-shaped intrauterine device with a cylinder containing levonorgestrel which releases 20 microgram of levonorgestrel in 24 hours through a release rate controlling membrane³ and is effective for a duration of 5 years with proven efficacy. The IUCD is aimed at reducing some of the problems related to the copper releasing intrauterine devices. The present study was conducted to compare the effects of levonorgestrel

releasing (LNG) and copper releasing (Cu T) intrauterine devices on body iron stores, hemoglobin and menstrual bleeding patterns in Indian women.

Patients and Methods

A total of hundred women attending the family planning clinic were included in this prospective observational study where LNG and Cu T was inserted for fifty women each according to their own choice after counseling for both methods. Women between the age group of 18-38 years, having at least previous one pregnancy and who had not used oral contraceptive or other hormonal preparation within last 6 months were included in this study. An informed consent was obtained for all patients after recruitment. Women with suspected pregnancy, previous ectopic pregnancy, pelvic inflammatory disease, lower genital tract infection, malignancy of cervix, uterus or adnexa or with any other pelvic tumor, endometrial polyp, vaginal bleeding of undiagnosed etiology, nulliparous or post menopausal women or with distortions of uterine cavity due to fibroids or congenital malformation, acute liver disease, liver tumor, severe cardiovascular disease or severe hypertension were excluded from this study.

After recruitment, thorough history was taken and complete physical examination including pelvic examination was done. Cu T was inserted in the post menstrual phase or during lactational amenorrhea using the no touch withdrawal technique. Loading of LNG was done by pulling on both the threads to draw the system into the insertion tube. The threads were fixed in the cleft at the near end of the inserter shaft. A special slider was provided for release of IUS. The intrauterine system was released by pulling down the slider all the way back and the threads were cut approximately 2 to 2.5 cm from the external os.

After insertion first follow up was done immediately after the next menstrual period to check for the position of IUCD and any complaints by the patient like pain or excessive bleeding and vaginal discharge were recorded. All patients were instructed to maintain menstrual diaries. Subsequent visits were done at the interval of 3, 6 and 12 months. In each of these visits, change

in menstrual bleeding patterns with respect to number of menstrual bleeding days and spotting days were noted and hematological investigations including hemoglobin, hematocrit, red cell count, mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration and serum ferritin were performed. Main outcome measures were serum ferritin, hemoglobin concentration, menstrual bleeding and spotting days 12 months after insertion.

Statistical Analysis

Descriptive statistics such as mean, standard deviation etc. have been used to summarize the baseline clinical and demographic profile of the patients. Repeated measure ANOVA was applied to see the mean difference among various quantifiable variables within each group respectively, whereas unpaired 't' was used to see the mean significant difference between the groups among various quantifiable variables. A p value < 0.05 was considered as significant. All statistical analysis was carried out using statistical package SPSS 11.5 (SPSS Inc., Chicago, IL, USA).

Results

All women participating in the study were between the age groups of 18 and 39 years. Majority of women were in the age group of 20-29 years in both the groups. Mean age was 26.2 years in the LNG and 24.5 years in the Cu T group. The mean parity was 1.9 in LNG and 1.4 in Cu T group patients. Most insertions in both groups were done postmenstrually or in the postpartum period.

Details of the number of days of bleeding in both groups are shown in Table I. In the LNG group it was observed that there was a significant increase ($p < 0.05$) in the number of bleeding days from 4.94 ± 1.609 to 6.42 ± 1.311 days after three months of insertion. The number of bleeding days reduced after 3 months and by the end of six ($p < 0.05$) and twelve months ($p < 0.000$) there was a significant decrease in the number of bleeding days as compared to pre insertion. A significant increase ($p < 0.05$) in the number of bleeding days was observed after insertion of Cu T during first three months (4.46 ± 0.908 to 5.70 ± 0.995 days) after which it reduced with only a minimal increase at the end of twelve months. This increase in the number of bleeding days be-

Table I. Comparison of number of bleeding days between Cu T and LNG.

Time of evaluation of bleeding days	Cu T 200	LNG-20	p-value
Pre-insertion	4.46 ± 0.908	4.94 ± 1.609	0.07
Three months	5.70 ± 0.995	6.42 ± 1.311	0.003
Six months	5.00 ± 1.161	4.34 ± 1.303	0.009
Twelve months	4.76 ± 0.960	3.14 ± 1.726	<.0001

fore insertion and after the end of one year (4.46 ± 0.908 to 4.76 ± 0.960 days) was not statistically significant ($p = \text{NS}$). On comparing the bleeding days between LNG and Cu T group, number of bleeding days were significantly more for Cu T vs. LNG group at the end of 6 and 12 months.

On comparing the number of days of spotting for both IUCD's (Table II) it was observed that before insertion there was no significant difference in number of spotting days between the two groups but by three and six months there was significant increase ($p < 0.0001$) i.e. number of spotting days increased in LNG group at three and six months as compared to Cu T group. However, at twelve months numbers of spotting days were more in Cu T group ($p < 0.05$).

There was increase in hemoglobin, red blood cells, packed cell volume, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration and serum ferritin at one year post insertion in LNG group (Table III). Table IV shows that there was decrease in hemoglobin, red blood corpuscles, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration and serum ferritin at twelve months as compared to pre-insertion in patients using Cu T.

No statistically significant difference in hemoglobin concentration between pre insertion and at three months between two groups was noted (Table V). However, there was a statistically significant increase ($p < 0.0001$) in hemoglobin concentration at six and twelve months after the insertion of LNG 20 vs. Cu T.

Table VI depicts that there was no statistically significant difference in serum ferritin before insertion and at three months but serum ferritin was significantly more ($p < 0.05$) at six and twelve months for LNG as compared to Cu T intrauterine device.

Discussion

Provision of an ideal contraceptive to a reproductive age female still continues to pose a major challenge to obstetrician. Despite the contraceptive protection achieved by copper medicated intrauterine devices, bleeding still remains the single most common cause for removal of an intrauterine device. The levonorgestrel releasing intrauterine device has provided a new dimension in intrauterine contraception. The most outstanding features of levonorgestrel releasing intrauterine device are its high contraceptive efficacy and reduction in menstrual blood flow⁴⁻⁷.

In the present study, we evaluated and compared the effect of LNG and Cu T releasing intrauterine device on menstrual bleeding patterns and iron stores of the body. In copper releasing IUCD group, there was a significant increase ($p < 0.05$) in number of menstrual bleeding and spotting days at three and six months but there was a non significant increase at twelve month as compared to pre insertion level. There was a significant decrease ($p < 0.05$) in serum ferritin at twelve months as compared to pre insertion lev-

Table II. Comparison of number of spotting days between Cu T and LNG.

Time of evaluation of spotting days	Cu T 200	LNG-20	p-value
Pre-insertion	0.38 ± 0.667	0.44 ± 0.787	0.682
Three months	3.83 ± 0.976	8.16 ± 1.754	< 0.0001
Six months	3.36 ± 0.921	4.96 ± 0.927	< 0.0001
Twelve months	1.78 ± 0.737	1.36 ± 0.985	< 0.05

Levonorgestrel vs. Cu T for iron stores and bleeding patterns

Table III. The hematological changes during the first year of insertion of levonorgestrel releasing intrauterine device (LNG-20).

Hematological parameter	Pre-insertion (mean $\pm$ SD)	Three months (mean $\pm$ SD)	Six months (mean $\pm$ SD)	Twelve months (mean $\pm$ SD)
Hb (gm/dl)	12.07 $\pm$ 0.55	11.40 $\pm$ 0.54	12.04 $\pm$ 0.49	12.44 $\pm$ 0.46
RBCs (million/ μ L)	4.019 $\pm$ 0.185	3.787 $\pm$ 0.186	4.016 $\pm$ 0.156	4.144 $\pm$ 0.151
PCV (%)	36.22 $\pm$ 1.667	34.356 $\pm$ 1.581	36.126 $\pm$ 1.49	37.272 $\pm$ 1.354
MCV (cubic micron)	90.097 $\pm$ 0.213	90.099 $\pm$ 0.058	89.94 $\pm$ 0.405	90.156 $\pm$ 0.285
MCH (Pico gram)	30.033 $\pm$ 0.017	30.033 $\pm$ 0.017	29.98 $\pm$ 0.177	30.035 $\pm$ 0.016
MCHC (%)	32.95 $\pm$ 0.357	32.655 $\pm$ 0.683	32.718 $\pm$ 1.508	33.301 $\pm$ 0.279
S. Ferritin (ng/ml)	23.522 $\pm$ 5.67	22.902 $\pm$ 5.75	24.67 $\pm$ 6.289	24.172 $\pm$ 5.971

Table IV. The hematological changes during the first year of insertion of Copper releasing intrauterine device (Cu T 200).

Hematological parameter	Pre-insertion (mean $\pm$ SD)	Three months (mean $\pm$ SD)	Six months (mean $\pm$ SD)	Twelve months (mean $\pm$ SD)
Hb (gm/dl)	11.95 $\pm$ 0.658	11.40 $\pm$ 0.5846	11.272 $\pm$ 0.6027	11.042 $\pm$ 0.568
RBCs (million/ μ L)	3.97 $\pm$ 0.219	3.814 $\pm$ 0.213	3.753 $\pm$ 0.201	3.68 $\pm$ 0.181
PCV (%)	35.85 $\pm$ 1.974	34.350 $\pm$ 1.850	33.816 $\pm$ 1.8082	33.142 $\pm$ 1.6602
MCV (cubic micron)	90.16 $\pm$ 0.139	90.035 $\pm$ 0.154	90.10 $\pm$ 0.070	90.026 $\pm$ 0.203
MCH (Pico gram)	30.03 $\pm$ 0.018	30.001 $\pm$ 0.059	31.35 $\pm$ 1.491	29.930 $\pm$ 0.272
MCHC (%)	33.33 $\pm$ 0.00	33.33 $\pm$ 0.00	32.97 $\pm$ 0.32	32.986 $\pm$ 0.235
S.Ferritin (ng/ml)	21.646 $\pm$ 5.77	20.986 $\pm$ 5.965	20.520 $\pm$ 5.952	20.801 $\pm$ 5.779

Table V. Comparison of hemoglobin concentration at pre-insertion, three, six and twelve months between two groups.

Time of evaluation of hemoglobin (g/dl)	Cu T 200	LNG 20	p-value
Pre-insertion	11.95 $\pm$ 0.658	12.07 $\pm$ 0.556	0.311
Three month	11.406 $\pm$ 0.584	11.444 $\pm$ 0.547	0.738
Six month	11.272 $\pm$ 0.6027	12.042 $\pm$ 0.4970	< 0.0001
Twelve month	11.042 $\pm$ 0.5628	12.448 $\pm$ 0.4608	< 0.0001

Table VI. Comparison of serum ferritin at pre-insertion, three, six and twelve months between two groups.

Time of evaluation of serum ferritin (ng/ml)	Cu T 200	LNG 20	p-value Cu T vs. LNG
Pre-insertion	21.646 $\pm$ 5.777	23.522 $\pm$ 5.673	0.105
Three month	20.986 $\pm$ 5.965	22.902 $\pm$ 5.753	0.105
Six month	20.520 $\pm$ 5.952	24.678 $\pm$ 6.289	0.001
Twelve month	20.801 $\pm$ 5.779	24.172 $\pm$ 5.971	0.05

el. These changes in menstrual bleeding pattern and serum ferritin were also reported by Heikkeliä et al⁸ and Andersson et al⁹.

In LNG group, the number of bleeding days were increased at three month of insertion ($p < 0.05$), there after it started decreasing and by the end of twelve month, some women became hypomenorrheic and amenorrheic. Similarly maximum number of spotting days increased at three and six months but at the end of twelve months there was a decrease in number of spotting days. Similar results were reported by Heikkeliä et al⁸ and Andersson et al⁹.

In women using LNG IUCD there was significant increase in serum ferritin at twelve month post insertion as compared to pre-insertion levels. Heikkeliä et al⁸ and Andersson et al⁹ reported similar increase in serum ferritin in women using LNG IUD at twelve month post insertion. Xiao et al¹⁰ reported a significant increase in hemoglobin from 12.15 g/dl pre-insertion to 13.55 g/dl after twelve months. The local effect of levonorgestrel on the endometrium leads to reduction of menstrual blood loss and to oligomenorrhea. The nature of this endometrial amenorrhea should be included in the information which is given to the women before insertion of LNG IUD to prevent uncertainties about pregnancy and later return to fertility.

Because iron deficiency seems to be the only condition associated with decrease in serum ferritin concentrations, our findings indicate that the use of conventional IUD, without iron supplement leads to a decrease in body iron stores. On the other hand, use of LNG releasing IUD was associated with a slight increase in the mean concentration of serum ferritin. In the present study the mean serum ferritin concentration decreased during the first six months in both the groups but in the levonorgestrel releasing intrauterine group it reached a plateau and in the copper releasing group it continued to decrease. At twelve months there was a significant difference in serum ferritin concentration between the two groups ($p < 0.05$) with decreased level in copper-T group.

In conclusion, the levonorgestrel releasing intrauterine devices reduce the blood loss and increase the hemoglobin levels and serum ferritin,

thus, prevents the loss of body iron stores. This may be especially important for women in developing countries like India where poor nutrition and diseases may contribute to iron deficient situations.

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