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REPRODUCCIÓN ASISTIDA EN ESPAÑA: INDICADORES, IMPACTO Y CONTEXTO SOCIODEMOGRÁFICO

Evgeniya Borisova

Doctorado en Demografía

TESIS DOCTORAL

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Decidí dedicar esta tesis doctoral a mi Maestro, Daniel Devolder.
El día de hoy deseo honrar su vida a través de esta dedicatoria.

Agradecimientos.

"A la espera de un milagro, aunque llegue con retraso
¡Cuántas veces este tiempo nos ha robado un recuerdo!"

Laura Pausini

He llegado al final de este periodo de mi vida que ha durado 7 años. Cuando comencé el Máster en Estudios Territoriales y de la Población (Especialidad Demografía), allá, por el año 2016, ya imaginaba que algún día podría conseguir mi sueño de ser Doctora en Demografía. Tras muchos años de sentir, manifestar y vivir una inmensidad de emociones distintas, ha llegado el momento en el que este pequeño sueño se cumple.

En el periodo de desarrollo de la tesis ha habido numerosos cambios: hemos pasado el tiempo de pandemia, jubilación del primer director de la tesis y su migración a otro continente, nacimiento de dos niñas preciosas…

Y, obviamente, ha habido muchas personas, sin las cuales esta tesis doctoral jamás hubiese visto la luz.

Mi primer agradecimiento lo dirijo al padrino de esta tesis, mi primer director, Dr. Daniel Devolder. Gracias por haber decidido ser mi director, gracias por confiar en mí. Agradezco cada momento de tu apoyo tanto profesional, cómo personal. Tú apostaste por mí y me enseñaste que las cosas se consiguen con esfuerzo y humildad. Agradezco las grandes ideas y cuestiones que has planteado y que han resultado fundamentales en la consecución de esta tesis doctoral. Durante estos años, más que un profesor has sido un amigo, al menos así te considero y, a pesar de que ha habido momentos diferentes durante estos años, siempre has estado aquí para ayudarme y apoyarme. Nunca dejaré de estar agradecida por esto.

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En tercer lugar, quiero expresar mi agradecimiento a la Universidad Autónoma de Barcelona (UAB) por brindarme la oportunidad de realizar mis estudios. También quiero dar gracias a todos los miembros del Centro de Estudios Demográficos (CED), que siempre han sido muy amables conmigo: Inés, Loli, Juan Antonio, Toni, Anna, Marc, Joan. Al mismo tiempo agradezco a todos mis compañeros del doctorado que siempre están dispuestos a hacer todo lo posible para ayudarme y apoyarme: Jianji, Laura, Paula, Maida, Parminder, Octavio, Nicolás, Carloa, Anna. Siempre nos quedarán las bonitas charlas de los ratos libres.

Por supuesto, me gustaría nombrar a mis amigos, que ya son una parte fundamental de mí. Con vosotros compartí los mejores momentos durante el desarrollo de la tesis: mi amiga rusa Zhanna, mis amigas catalanas Sandra y Mercè, mi amiga canaria Inma y mi grupo del Camino de Santiago (19 personas). No puedo estar más agradecida de haber conocido a personas tan únicas. Espero que nuestra relación de amistad no se rompa nunca y que podamos seguir disfrutando juntos. Gracias, gracias, muchas gracias.

El final de estos agradecimientos quiero destinarlo a mi familia. A mi madre, que, aunque está lejos, siempre está conmigo. Gracias por nunca dejar de creer en mí, quererme como soy y siempre animarme de seguir mis sueños.

Quiero darle las gracias a mi marido, Roberto, por todo el apoyo que me ha brindado a lo largo de este proceso. Sin tu ayuda, no hubiera podido terminar mi tesis. Quiero agradecerte por ser mi confidente y amigo, y por soportarme durante todos estos años. Especialmente el último año fue el más feliz para nosotros por el nacimiento de Beatriz, pero al mismo tiempo, el más duro, porque lo afrontamos sin ningún tipo de ayuda. Sin duda, eres una de las personas que más conoce las distintas emociones que han aflorado durante este periodo y, por tanto, quien más ha compartido conmigo los mejores y peores momentos. Sabes que estoy muy agradecida de todo el apoyo que me das y de que me hagas sentir especial.

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CAPÍTULO I: Introducción

"La belleza no tiene edad. La fertilidad sí."

El eslogan fue ideado por el Ministerio de Sanidad italiano

Durante la segunda mitad del siglo XX y las primeras décadas del siglo XXI la población mundial ha experimentado una verdadera revolución en términos demográficos. Uno de los cambios más remarcables ha sido el descenso de los indicadores sintéticos de fecundidad. Según los datos de Naciones Unidas (2022), el indicador de fecundidad ha pasado de 5 hijos por mujer en los años 50 del siglo pasado hasta 2,3 hijos por mujer en el año 2021. Durante el mismo período, Europa se encontraba en una fase más avanzada del proceso de transición demográfica y experimentó un descenso menos pronunciado, pasando de 2,6 hijos por mujer hasta 1,5 hijos.

Este proceso de caída de la fecundidad se ha dado también en España de forma más acelerada y aguda. El número medio de hijos por mujer pasó de 2,8 en los años de "baby-boom (los años 1958-1976) a valores inferiores a 1,5 hijos de forma sostenida desde 1987 hasta la actualidad. Este régimen de baja fecundidad alcanzó su máximo histórico durante la década 1993-2003 durante la cual la tasa global se mantuvo por debajo de 1,3 hijos, algo excepcional en el mundo y que recibe el calificativo de régimen de muy baja fecundidad –"lowest low fertility"- (Kohler et. al. 2002).

La tendencia de la reducción de la tasa de fecundidad tiene implicaciones demográficas y socioeconómicas. Junto con la mejora de la longevidad, son la causa del envejecimiento demográfico que supone el incremento del peso relativo de los mayores en la estructura poblacional. La tendencia de retrasar la edad a la maternidad también conlleva consecuencias en la salud de la mujer: dificulta las posibilidades de concebir a partir de los 35 años por el descenso de fertilidad, aumenta la tasa de multiplicidad de partos y puede aumentar la probabilidad de abortos espontáneos. Por este motivo, el retraso del calendario reproductivo también ha supuesto un incremento sustancial del uso de técnicas de reproducción asistida.

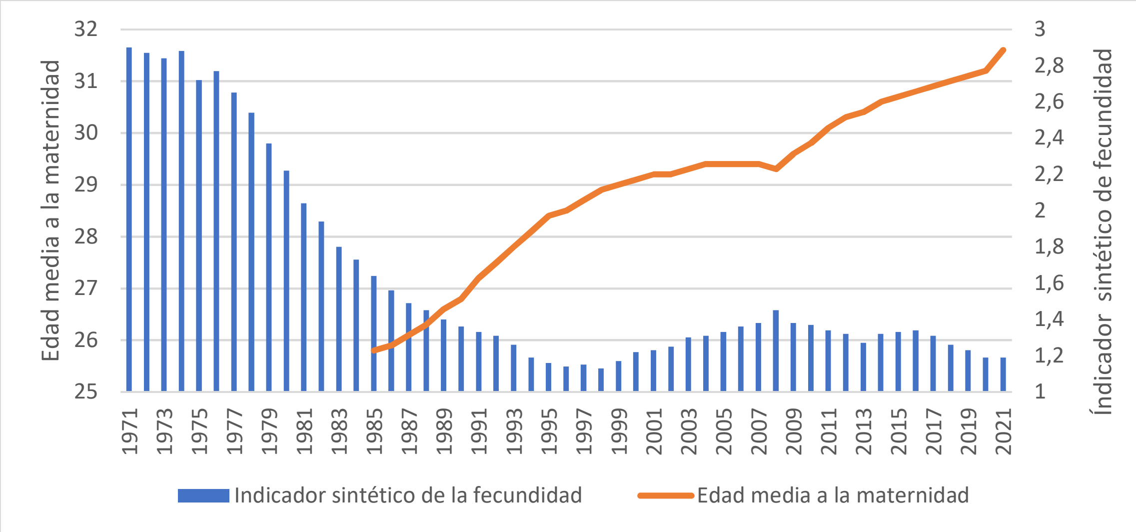
Esta tesis doctoral aborda el estudio del uso de las técnicas de reproducción asistida mediante una aproximación cuantitativa con el objetivo de entender el alcance de su impacto demográfico, los nuevos indicadores del éxito de los tratamientos así como los determinantes sociales que explican su expansión. Desde un punto de vista social, es crucial entender de qué forma las opciones reproductivas de hombres y mujeres se han visto modificadas al abrirse nuevas oportunidades gracias a los avances médicos. Recíprocamente, desde un punto de vista médico, es de gran relevancia entender los procesos sociales y demográficos que motivan las nuevas necesidades de los pacientes que acuden a la reproducción asistida.

Los resultados del estudio del impacto de la reproducción asistida son relevantes para la salud pública y política sanitaria, puesto que permiten evaluar los efectos médicos y sociales de ofrecer cobertura amplia o restringida a dichas técnicas por parte de la legislación y los sistemas sanitarios. Los resultados también permiten contribuir al debate abierto en el campo de la demografía y la sociología de la familia sobre las nuevas formas de desigualdad en las dinámicas demográficas y los comportamientos familiares. Por último, y no menos importante, entender los mecanismos legales, técnicos e individuales que explican el acceso y uso de la reproducción asistida, así como sus resultados en términos de nacimientos, ofrece elementos clave para comprender de qué manera van a evolucionar en el futuro, la reproducción humana, el crecimiento demográfico y las relaciones de filiación.

El trabajo se centra en el caso de España, que es excepcional tanto por el régimen demográfico de baja fecundidad y retraso de la edad a la maternidad como por la intensidad en el uso de la reproducción asistida. Por un lado, la edad media a la primera maternidad en España aumentó de los 26 años en 1985 a los 31,2 años en 2020 (ver figure 1-1). Según la Teoría de la Segunda Transición Demográfica, el retraso del calendario reproductivo está relacionado con el retraso de la nupcialidad y la formación de parejas estables, las transformaciones de las estructuras familiares y la difusión de la cohabitación no matrimonial (Davia, y Legazpe 2014). Sin embargo, especialmente para el caso de España, los factores más explicativos del retraso se encuentran en las incertidumbres económicas y laborales que dificultan alcanzar estabilidad residencial y laboral y posponen la emancipación de los jóvenes. Por este motivo analizar la evolución reciente en España supone una contribución importante al campo de los estudios de fecundidad.

Por otro lado, España tiene uno de los mayores porcentajes de nacimientos que son resultados de técnicas de reproducción asistida, entre un 8% en 2019 (Devolder & Borisova, 2022) y el 9,2% en 2018 (Goisis, et al. 2023). En parte, como veremos a continuación, esta excepcionalidad se explica porque el acceso a la reproducción asistida dispone de un marco legislativo poco restrictivo y que ofrece amplia cobertura de la sanidad pública.

Figure 1-1. Indicador sintético de fecundidad y edad media a la primera maternidad. España 1971-2021



Fuente. Eurostat. Elaboración propia.

En este capítulo introductorio presentamos los conceptos y tendencias recientes de infertilidad y uso de técnicas de reproducción asistida con el objeto de proveer el marco interpretativo necesario para los análisis que realiza la investigación doctoral. A continuación, formulamos los objetivos de la tesis y presentamos su estructura detallando el contenido de los distintos capítulos.

1.1 Infecundidad e infertilidad

El cambio demográfico y el retraso y caída de la fecundidad han llevado aparejados un incremento del porcentaje de mujeres que acaban sus vidas reproductivas sin haber tenido hijos. Es lo que en demografía denominamos infecundidad. Es esencial distinguir entre aquellas mujeres que no pueden tenerlos por razones biológicas y que experimentan "una infecundidad involuntaria" o, en términos médicos, una "infertilidad primaria" y aquellas mujeres que sí pueden tener hijos, pero no los desean, eso es "infecundidad voluntaria"[1]. En castellano hasta hace unos años se diferenciaban los términos "esterilidad" como dificultad de conseguir el embarazo e "infertilidad" como dificultad para conseguir que el embarazo concluyera en un nacimiento. En la actualidad el Diccionario de la Real Academia Española los considera como sinónimos, como la "incapacidad de un ser humano para reproducirse".

Dentro de la infecundidad involuntaria es clave el papel del retraso ya que la vida fértil de las mujeres está acotada y su infertilidad aumenta significativamente con la edad de la mujer. Desde el punto de vista de la salud reproductiva, con el retraso de la edad reproductiva también aparecen más patologías ginecológicas: endometriosis, miomas, cáncer. Como veremos a continuación también son mayores las probabilidades de una interrupción espontánea de la gestación y de un parto múltiple.

Por este motivo, las mujeres que retrasaron su edad a la entrada a la maternidad más allá de los 35 años por esperar las condiciones económicas y familiares adecuadas se enfrentan a mayores riesgos de infertilidad y ponen en riesgo su potencial reproductivo (Esteve, Devolder y Domingo, 2016). Y por este motivo la infertilidad se ha convertido en un problema bastante frecuente en nuestra sociedad. Según los datos de OMS (Organización Mundial de Salud), la infertilidad afecta a millones de personas en todo el mundo, de esta enfermedad sufren unos 48 millones de parejas y unos 186 millones de personas.

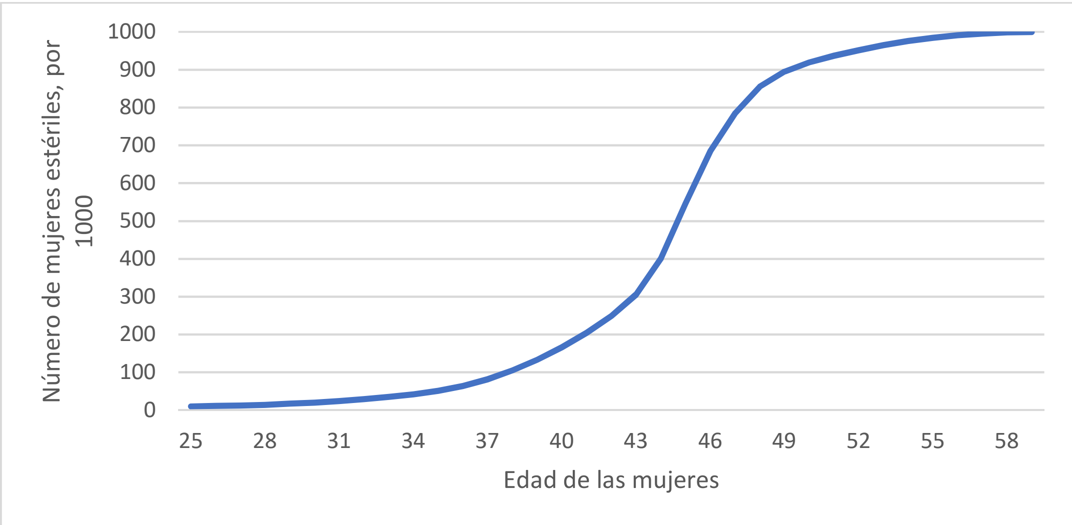
La infertilidad se puede clasificar en dos grandes grupos: la primaria y la secundaria. Infertilidad primaria significa que la pareja nunca ha podido lograr una concepción mientras que la secundaria aplica a las parejas que alguna vez han tenido un embarazo pero que a partir de un cierto momento ya no pueden volver a concebir. Se estima que de las mujeres de entre 20 y 44 años expuestas a riesgo de embarazarse (con relaciones sexuales sin protección) el 2% sufren infertilidad primaria y el 10% infertilidad secundaria (Mascarenhas et al. 2012). La infertilidad puede ser femenina, masculina, de

[1] Hay que tener en cuenta que los términos "esterilidad", infertilidad" y "infecundidad" no tienen el mismo significado en el campo médico y en la demografía. En medicina el término "esterilidad" significa incapacidad del cuerpo humano (tanto masculino, como femenino) a producir gametocitos. El término "infecundidad" significa que hay gametos, pero algo impide su conjunción e impide la fecundación. "Infertilidad" significa que los gametos se juntaron, ha pasado el periodo de la fecundación, pero por algún motivo el embrión no llega hasta el nacimiento y se expulsa. En cambio, para la demografía, la "infertilidad" es la incapacidad de tener hijos y la "infecundidad" al hecho de no haber tenido hijos (Matorras 2011).

ambos o ser de origen desconocido. Se estima que alrededor de 40% de los casos de infertilidad son de causa masculina, otro 40% se debe a causas femeninas. Y el 20% restante corresponde a causas mixtas o combinadas (Vidal, 2001).

La investigación sobre la influencia de la edad de mujeres sobre la fertilidad es amplia. De acuerdo con la evidencia científica, como se muestra en el figure 1-2, después de los 35 años la fertilidad disminuye y sube el número de mujeres estériles. Además del determinante de la edad de la mujer, otros factores explican los niveles de infertilidad y su tendencia creciente. En primer lugar, hay que considerar también la infertilidad masculina, en segundo lugar, los nuevos estilos de vida que podrían estar generando nuevas alteraciones en la capacidad reproductiva tanto de hombres como de mujeres y finalmente los factores ambientales como la presencia de determinadas sustancias químicas y o tóxicas con efectos en la reproducción (Seiz et al. 2023).

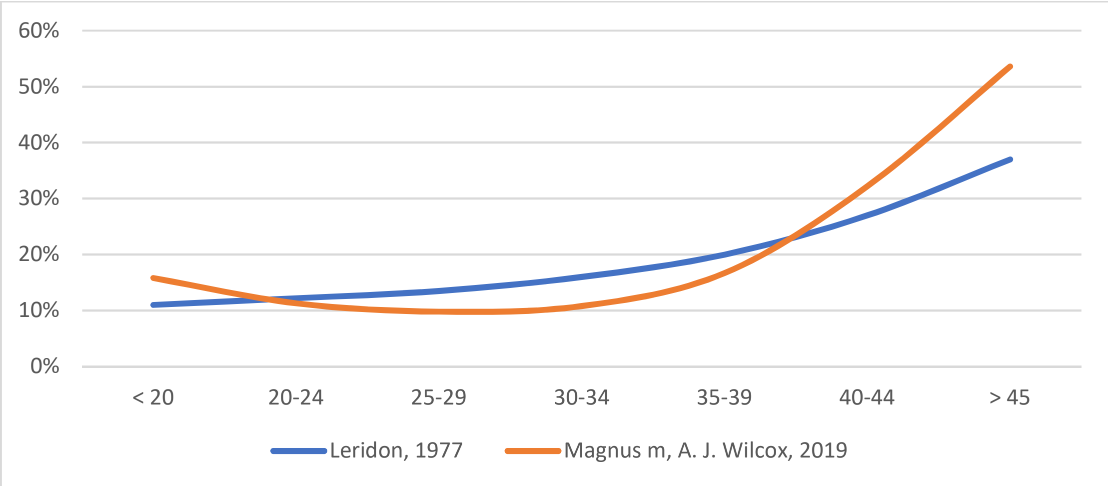
Figure 1-2 Número (por 1 000) de mujeres estériles por la edad: estimación según el modelo de Léridon, 2008ª



Fuente: Léridon 2008ª.

Desde un punto de vista médico, el retraso del calendario reproductivo no solo reduce las probabilidades de una concepción, sino que también aumenta el riesgo de que los embarazos no culminen en un nacimiento. En concreto, como se muestra en el figure 1-3, el riesgo del aborto aumenta con la edad de la mujer. Según los estudios clásicos de Léridon (1977), el riesgo del aborto para las mujeres de 37 años es 20%, el riesgo para la mujer de 44 es 30%. Magnus y Wilcox (2019) en su artículo descubrieron, que el riesgo del aborto es más bajo para las mujeres de 20-34 años (10-11%) y el mayor riesgo es a partir de 45 años (de 53%). Las mujeres jóvenes (menos de 20 años) tienen el riesgo del aborto 15,8%.

Figure 1-3. El riesgo del aborto según la edad de la mujer



Fuente: Elaboración propia a partir de M.Magnus, A.J. Wilcox, et. al (2019) y Leridon (1977).

Hay que considerar como otra consecuencia indeseable del retraso de la edad a la maternidad el mayor riesgo de partos múltiples. En concreto, esto depende de los niveles de la hormona folículo-estimulante (FSH), que es la responsable de la ovulación múltiple cuanto mayor es la edad de la mujer. Waterhouse (1950) en una investigación basada en el método del Weinberg (1902), mostró que la probabilidad de tener mellizos dicigóticos (los que provienen de diferentes óvulos) aumenta con la edad de la madre, llega a su máximo en las edades 35-39 años, y después cae rápido. Así, como se muestra en el Capítulo III (figure 3-2), a los 36-37 años la probabilidad de tener un embarazo múltiple sube mucho. Sin embargo, aunque la probabilidad de tener mellizos dicigóticos aumenta con la edad de la madre, la probabilidad de tener gemelos monocigóticos es constante para todas las edades.

La incidencia de partos múltiples conlleva muchos problemas para la salud de la madre y de los bebés. Estudios de la multiplicidad afirman la existencia de altos riesgos. Por ejemplo, Bulmer (1970) en su libro afirma que los embarazos múltiples tienen muchas complicaciones, los bebés nacen con más frecuencia con el peso bajo y prematuros. También hay mayor riesgo de que uno o varios bebés padezcan problemas en desarrollo postnatal y aumenta la probabilidad de muerte de la madre o de los bebés. Aunque muchos padres prefieren tener mellizos y gemelos hay que tener en cuenta que el riesgo de padecer problemas de salud es más alto.

Considerando que los estudios han mostrado la existencia de una asociación entre la edad avanzada de la mujer esterilidad, y riesgo de aborto espontáneo, y posibilidad de tener complicaciones en partos múltiples de alto riesgo, algunos autores advierten del exceso de confianza de algunas mujeres y parejas en las posibilidades de la reproducción asistida, lo que las lleva a posponer ignorando los efectos de la edad en la fertilidad (Mills et al. 2015).

1.2 Reproducción asistida

Esta nueva realidad social de retraso de la maternidad e infecundidad creciente, junto con los progresos en el campo médico y científico, han dado lugar al desarrollo de novedosas soluciones tecnológicas que permiten conseguir un embarazo a mujeres y parejas con dificultades para concebir de forma natural. A continuación, presentamos: a) la tipología de estas técnicas, b) los marcos reguladores vigentes en cuanto al acceso y uso, y, c) su grado de eficacia.

El concepto de "técnicas de reproducción asistida" (TRA) se refiere a las técnicas de alta complejidad que incluyen el manejo in vitro tanto de óvulos como de espermatozoides o de embriones para la finalidad de reproducción. Estas técnicas son: la fecundación in vitro (FIV), inyección intracitoplasmática de espermatozoides (ICSI), y la transferencia de embriones (ET), la transferencia intratubárica de gametos (GIFT), la transferencia intratubárica de zigotos, la transferencia intratubárica de embriones, la criopreservación de ovocitos y embriones, la donación de ovocitos y embriones, y el útero subrogado. (Zegers-Hochschild F. et. al., 2017).

El término más amplio reproducción medicamente asistida (MAR, según las siglas en inglés) refiere a varias intervenciones para tratar diferentes formas de infertilidad, incluyendo todas las formas de TRA, pero también otros tratamientos: inseminación artificial (IA) con semen del esposo/pareja o donante, inducción de la ovulación y estimulación ovárica (Zegers-Hochschild et al., 2017). En esta tesis también se tendrá en cuenta a veces el impacto de estas técnicas relacionadas como la inseminación artificial (IA) y el coito programado (CP) porque, aunque no tienen como propósito directo resolver los problemas de esterilidad o subfecundidad aguda de las parejas, sí tienen un impacto sobre la natalidad y la fecundidad, y notablemente sobre la multiplicidad de los partos porque se asocian con el uso de fármacos que estimulan la ovulación.

Hace más de 40 años que se aplican técnicas de reproducción asistida y se estima que la práctica de intervenciones como la fecundación *in vitro* ha permitido dar a luz a más de 5 millones de niños en todo el mundo. Las técnicas de reproducción asistida han evolucionado de forma radical en las últimas décadas en los países occidentales. Se han desarrollado nuevas técnicas, se ha mejorado su eficacia y se ha legislado para regular su uso y acceso. También se ha transformado la valoración social del uso de dichas técnicas para conseguir un embarazo (Maroto-Navarro, 2004).

Sin embargo, en muchas partes del mundo, sobre todo en los países de ingresos medianos y bajos, estos servicios todavía no están disponibles o no son accesibles o asequibles. Incluso en el contexto europeo, la regulación de TRA no es homogénea entre los países. La legislación en la materia regula esencialmente tres aspectos esenciales: los criterios de elegibilidad para acceder a tratamientos; la disponibilidad de cobertura pública de los tratamientos y el grado de autonomía del que disponen los profesionales médicos. La combinación de estos tres aspectos da como resultado marcos más permisivos o más restrictivos, tal y como recoge en un indicador sintético el *Atlas europeo de las políticas de tratamiento de la fertilidad* (elaborado por las entidades Fertility Europe y European Parliamentary Forum for Sexual and Reproductive rights).

De acuerdo con este indicador, España obtiene uno de los valores más elevados en el contexto europeo y se caracteriza, por tanto, por una legislación particularmente progresista en la materia. Más adelante, en Capítulo II, con más detalle se describe la situación legislativa en España, pero la excepcionalidad introducida por la Ley 14/2006 radica en el acceso de todas las mujeres mayores de 18 años independiente de su estado civil y orientación sexual a las técnicas TRA y en autorización de la donación de gametos y preembriones.

En otros países, sin embargo, se restringe el acceso por razón de edad o estado civil de la mujer, o bien se limita a ciertos tratamientos y se prohíbe la donación de gametos y preembriones. Además de la regulación del acceso el otro factor esencial es el del grado de cobertura pública, que convierte al coste económico en un factor que, además del marco regulador propiamente dicho, acaba determinando el acceso a los tratamientos y el grado de demanda insatisfecha. Según los datos del informe que realiza IFFS Surveillance, en Francia, Bélgica, Italia, Estados Unidos el gobierno no paga por los tratamientos de infertilidad. Sin embargo, en los países como España y Rusia, la Seguridad Social reembolsa los gastos para las mujeres de hasta 40 años, pero las colas de espera pueden durar varios años y el acceso es limitado dependiendo de la edad de la mujer y el número de tratamientos.

Un efecto evidente de esta disparidad en la regulación y el acceso a la reproducción asistida en los distintos países es el desplazamiento de la demanda desde los países más restrictivos a los países más permisivos.

La disparidad en el acceso a los tratamientos también tiene implicaciones en las desigualdades sociales. Seiz et al (2023) muestran en su estudio comparado que el gradiente social (la mayor probabilidad de someterse a tratamiento de las mujeres con mayor educación y estatus socioeconómico) es más acentuado en los países en los que la cobertura pública es reducida y, por consiguiente, en los que los costes de los tratamientos son más elevados. Sin embargo, las mismas autoras también señalan que el gradiente social existe incluso en países con bajos costes, lo que sugiere que existen otros tipos de barreras además de las económicas, probablemente menos materiales y relacionadas con valores y preferencias.

La eficacia de tratamientos de la reproducción asistida varía en función de la técnica empleada (las técnicas de alta complejidad tienen mayor probabilidad de éxito), la edad de la mujer (con el aumento de la edad, disminuye el porcentaje del éxito), el tipo de infertilidad (primaria o secundaria) y del número de ciclos a los que se ha sometido (con más ciclos, más probabilidades de éxito). El registro europeo de la "European Society of Human Reproduction and Embriology (ESHRE) publica cada año información comparada para diversos países europeos que sugiere que las tasas de éxito de España (medidas como tasa de embarazo o tasa de parto) están en línea con las de la media de los países europeos (tabla 1-1).

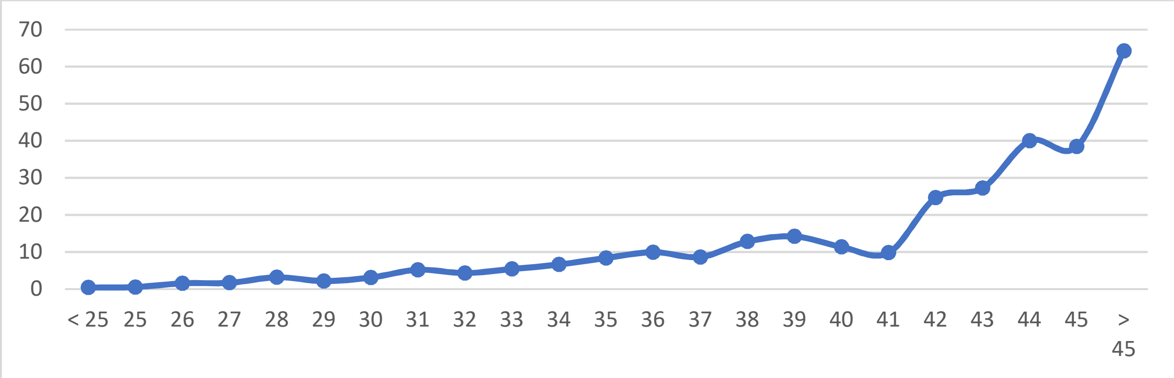
Tabla 1-1. Tasas de embarazo y de parto por edad de la mujer según tratamiento, España 2018

	Tasa de embarazo %			Tasa de parto %		
	<= 34 años	35-39	> 40 años	<= 34 años	35-39	> 40 años
FIV						
España	29.0	26.3	15.9	24.1	19.0	8.7
Europa	30.8	25.4	13.6	25.1	19.0	7.8
ICSI						
España	24.2	21.3	13.2	19.2	15.3	7.5
Europa	27.9	22.3	11.2	22.1	16.1	6.3
ET						
España	48.1	48.6	46.5	35.6	37.5	33.2
Europa	43.6	44.9	43.2	33.4	33.2	29.5
IA, marido						
España				10.8	9.8	8.7
Europa				6.4	5.6	2.3
IA, donante						
España				18.9	13.3	6.0
Europa				14.5	10.6	3.8

Fuente. European Society of Human Reproduction and Embriology (ESHRE), 2018

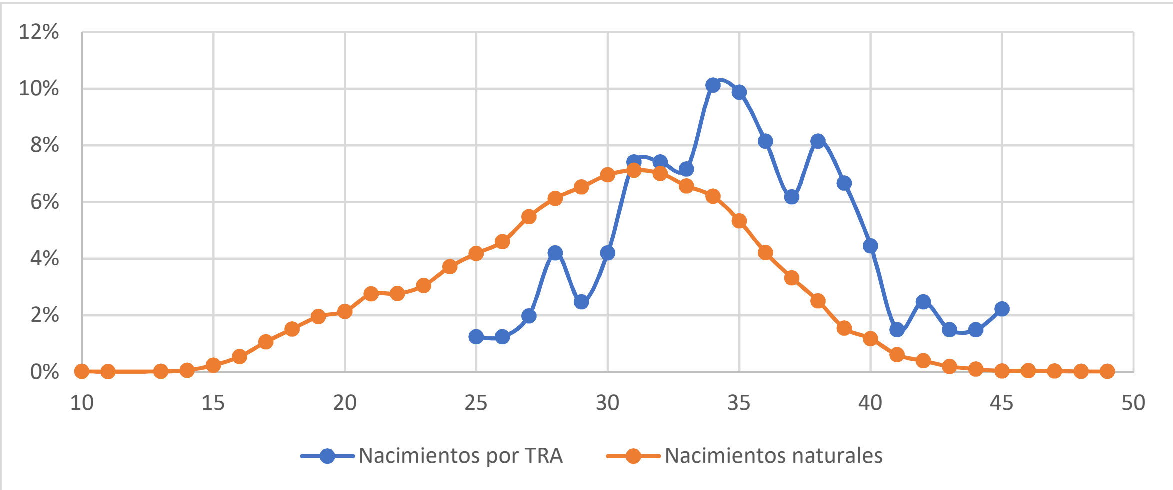
La combinación de las tasas crecientes de uso de reproducción asistida y de la también creciente tasa de éxito, da como resultado un impacto cada vez mayor en el número de nacimientos. Las implicaciones de fecundidad son evidentes y objeto de gran interés para los demógrafos. En un estudio reciente, Lazzari y colegas et al. (2023) estiman que si se mantuvieran las tasas de éxito y las tasas de tratamiento, la contribución de los nacimientos que resultan de la reproducción asistida sobre el total pasarían de representar el 2,1% para las mujeres nacidas en 1968 al 5,7% para las mujeres nacidas en 1986. También enfatizan su importancia para satisfacer los proyectos reproductivos en edades avanzadas. Para el caso de España, el gráfico 1-4 muestra que la mayoría de los nacimientos a partir de los 40 años de la edad de la madre se deben a las técnicas TRA. Correspondientemente, el gráfico 1-5 compara el calendario de los nacimientos con concepción natural y asistida mostrando que el calendario de los segundos es claramente más tardío que el de los primeros.

Figure 1-4. Porcentaje de partos por las TRA sobre el total por edad de la madre



Fuente. Elaboración propia. Encuesta de fecundidad (2018)

Figure 1-5. Distribución de los nacimientos según tipo de concepción y edad de la madre



Fuente. Elaboración propia. Encuesta de fecundidad (2018)

1.3 Objetivos y estructura de la tesis

Esta tesis doctoral se plantea los siguientes objetivos de investigación con el fin último de comprender los mecanismos que explican el uso de las técnicas de reproducción asistida y evaluar sus impactos reproductivos, demográficos y sociales. Para cada objetivo se formulan una serie de preguntas de investigación que guiarán el análisis

Objetivo 1. Analizar los cambios demográficos y sociales que han contribuido a un aumento de la demanda de asistencia médica para la reproducción.

- ¿Cuál es la relación entre el retraso de la fecundidad y las dificultades para concebir de forma natural con la demanda de asistencia?

Objetivo 2. Analizar las condiciones y las pautas de acceso a la reproducción asistida.

- ¿Existen desigualdades sociales y educativas en el acceso a las técnicas de reproducción asistida?
- ¿La cobertura ofrecida por el marco regulador determina el grado de satisfacción de la demanda potencial de asistencia?

Objetivo 3. Analizar los efectos reproductivos del uso de técnicas de asistencia reproductiva.

- ¿Las técnicas de reproducción asistida han contribuido al incremento de la multiplicidad de los partos?
- ¿Cuáles son las implicaciones del uso de las técnicas en la salud reproductiva de las madres?

Objetivo 4. Analizar los efectos en la natalidad del uso de técnicas de reproducción asistida.

- ¿En qué medida el uso de técnicas de reproducción asistida es un antídoto ante el retraso y la caída de la fecundidad?

Objetivo 5. Analizar el éxito de los distintos tratamientos y los factores que lo determinan.

- ¿Cuál es el mejor indicador para estimar el éxito de los tratamientos?
- ¿Qué determina la probabilidad de éxito de un tratamiento de fecundación in vitro?

Para alcanzar estos objetivos de investigación se analizarán datos secundarios de diversas fuentes de naturaleza distinta. Se combinará información procedente de registros (concretamente el registro de tratamientos de la Sociedad Española de Fertilidad (SEF) y registros comparables de otros países y de Cataluña), con datos demográficos y con datos de encuesta (Encuesta de Fecundidad 2018, Instituto Nacional de Estadística). En algunos capítulos en particular se hará un esfuerzo por discutir los indicadores estándares y hacer una contribución metodológica que permita mejorar la medición de la incidencia, el éxito y el impacto de los tratamientos de reproducción asistida. En conjunto, si bien la tesis analiza principalmente datos de España, se trabaja también con datos de otros países para ofrecer una visión comparada, siempre que esto sea posible.

La tesis se compone de este primer capítulo -la introducción-, 4 capítulos que se resumen brevemente a continuación y que culminan en un capítulo de conclusiones en las que se argumentan las principales contribuciones del trabajo, así como sus limitaciones y perspectivas de desarrollo para el futuro.

El segundo capítulo, ***"Demanda y acceso de reproducción asistida en España: diferenciales sociodemográficos"*** proviene de un artículo realizado junto a las Directoras de la Tesis Clara Cortina y Mariona Lozano. En él se analiza la demanda actual de tratamientos de reproducción asistida en España y se realiza una descripción del acceso a ellos. El análisis está basado en los datos de la Encuesta de Fecundidad española de 2018 y aplica técnicas estadísticas multivariadas. Los resultados muestran que las mujeres con un nivel socioeconómico más alto y sin hijos (infertilidad primaria) tienen una mayor probabilidad de someterse a tratamientos de reproducción asistida. Los resultados también apuntan a que las nuevas generaciones se someten a estos tratamientos con más frecuencia, y concluimos que ello podría deberse al retraso en la maternidad, el desarrollo de la calidad de las mismas técnicas, los cambios en las formas de familia y los avances en la legislación.

El tercer capítulo ***"Demographic impact of In vitro fertilization in Spain." (Devolder D., Borisova E.),*** ya publicado en la revista "Medicina reproductiva y Embriología clínica", reconstruye la serie de ciclos para el periodo 1999-2019 corrigiendo por la no participación para estimar el peso de los nacimientos por FIV en España. Esta estimación tiene en cuenta los embarazos de evolución desconocida, así como la demanda de las mujeres residentes en el extranjero. Se analizan los datos de Fecundación In Vitro (FIV) del registro de la Sociedad Española de Fertilidad (SEF), registros comparables de otros países y de Cataluña y, finalmente la Encuesta Española de Fecundidad de 2018. En el capítulo también se discute qué tipo de mejoras podrían hacer más útil este registro y los correspondientes informes realizados por la Sociedad Española de Fertilidad (SEF), a efectos de análisis demográfico y social, de cara a la transición a un registro individual en los próximos años.

El objetivo del cuarto capítulo, "***Standardisation and decomposition methods for measuring the effect of assisted reproduction on twinning and the birth rate: Spain in the period 1983–2020"*** es calcular el peso del efecto MAR (Medically assisted reproduction) en nacimientos múltiples y verificar los resultados de las estimaciones obtenidas en el capítulo anterior sobre el impacto de estos tratamientos en el número de nacimientos. Este artículo está hecho junto con Daniel Devolder y está pendiente para enviarlo a la revista. Para poder entender el efecto de las técnicas sobre la multiplicidad, veremos que se puede conseguir de tres distintas maneras, que aplicamos y comparamos: con los métodos de estandarización directa e indirecta, y con el uso del método de descomposición (Kitagawa, 1955 y extensiones) con mejoras que permitan mitigar su límite principal: los efectos del salto del tiempo continuo al discreto, siguiendo el planteamiento de Horiuchi et al. (2008). También utilizamos los datos de los registros de tratamientos y la Encuesta Española de Fecundidad de 2018 para verificar los resultados.

El quinto capítulo, "***Measuring In Vitro Fertilization success for each embryo transferred and detecting the effect of embryo synergy at an aggregate level***" proviene de un artículo realizado junto a Daniel Devolder D. y está pendiente para enviarlo a la revista. Se propone una nueva fórmula de medir el éxito de la fecundación-in-vitro (FIV) a nivel agregado, que podría complementar la Tasa de nacidos vivos (LBR). La propuesta radica, esencialmente, en tener en cuenta el número de embriones transferidos a la hora de estimar la eficacia. Se usan datos agregados de registros de TRA de diferentes países (Canadá, América Latina, Portugal, Rusia, España, Suiza, UK, US) integrados en un único modelo que agrupa los siguientes tratamientos: óvulos propios frescos, óvulos propios criopreservados, óvulos de donantes frescos y óvulos de donantes criopreservados. El indicador propuesto permite detectar el efecto de sinergia embrionaria, que sugiere que la implantación de dos embriones transferidos al mismo tiempo aumenta la probabilidad de supervivencia de un embrión.

CAPÍTULO II.- Demanda y acceso de reproducción asistida en España: diferenciales sociodemográficos[2]

"A una mujer que quiere ser madre, no hay nada que la pare."

Autora desconocida.

Resumen

En este capítulo se analiza la demanda actual de tratamientos de reproducción asistida en España, y se realiza una descripción a fondo del acceso a tales tratamientos. España tiene uno de los mayores porcentajes de nacimientos que son resultado de reproducción asistida en Europa. Sin embargo, hay pocos estudios sobre el perfil de las mujeres que usan estas técnicas y sobre las diferencias socioeconómicas en el acceso a ellas. En parte, ello es debido a la falta de datos hasta hace pocos años. Se utilizan los datos de la Encuesta de Fecundidad española de 2018 y se encuentra que las mujeres con un nivel socioeconómico más alto y sin hijos (infertilidad primaria) tienen una mayor probabilidad de someterse a tratamientos de reproducción asistida. Los resultados también apuntan a que las generaciones más jóvenes se someten a estos tratamientos con más frecuencia, y concluimos que ello podría deberse al retraso a la edad a la maternidad, el desarrollo de la calidad de las mismas técnicas, los cambios en las formas de familia y los avances en la legislación. Además, encontramos que la causa principal de no acceder a los tratamientos, aunque se reporta necesitar de ellos, es la situación económica, con lo que hay una demanda potencial de estos tratamientos no satisfecha. Aunque los tratamientos de reproducción asistida están cubiertos por la seguridad social para mujeres menores de 40 años, nuestros resultados apuntan que no todas tienen fácil acceso e hipotizamos que ello se debería a las largas listas de espera.

2.1 Introducción

En España, al igual que en otros países europeos, el aumento de la infecundidad y los desafíos para concebir entre parejas que desean tener hijos se asocian principalmente con la dilatación de las trayectorias familiares y la postergación de la edad al primer hijo (Del Rey et al. 2007). Ambas circunstancias están motivadas por la expansión del nivel educativo de las mujeres que, por un lado, induce a la incompatibilidad del rol de madre

[2] Este capítulo está realizado junto a las directoras de la tesis: Clara Cortina y Mariona Lozano

y estudiante; y por otro, a mayores aspiraciones en el terreno profesional, priorizándose las carreras laborales en las edades jóvenes, para facilitar, con posterioridad, la formación de una pareja y la asunción del coste de un hijo. Pero España, junto con Italia, es el país de la Unión Europea con la entrada a la maternidad más tardía y con una edad al nacimiento del primer hijo mayor, 31,6 años en 2021 según datos de Eurostat. Esta postergación hace que muchas mujeres empiecen sus proyectos reproductivos a edades en las que biológicamente es más difícil concebir de manera natural.

La evidencia actual indica que la prevalencia de la infertilidad, definida por los médicos como la incapacidad de lograr un embarazo después de 12 meses de relaciones sexuales regulares sin protección, es del 9%, con un 56% de parejas que buscan atención médica (Boivin et al., 2007). Esta última estimación es similar entre los países desarrollados, y esta prevalencia ha aumentado en comparación con estimaciones nacionales anteriores (De La Rochebrochard & Thonneau, 2005).

El uso de las técnicas de reproducción asistida ha aumentado en las últimas décadas en todo el mundo. Si hace 30 años existía una alta necesidad de ayuda médica para las parejas infértiles cuyo deseo de tener hijos quedaba insatisfecho por las dificultades de acceso (Olsen et al. M, 1996), actualmente más mujeres pueden acceder a estos tratamientos debido a la proliferación de clínicas de tratamientos de la infertilidad y a la cobertura de estos tratamientos por parte de la sanidad pública. La reproducción asistida es una herramienta importante para la satisfacción de los proyectos reproductivos y tienen implicaciones para los niveles de fecundidad (Lazzari et al. 2021). En España, el uso de la reproducción asistida ha crecido de forma significativa y actualmente se sitúa como el país europeo en el que el porcentaje de nacimientos que resultan de tratamiento es más elevado, un 6,4% en 2018 (Passet-Wittig & Bujard 2021) y un 8% en 2019 (Devolder & Borisova, 2022). Sin embargo, disponemos de muy pocos estudios sobre el uso actual de estas técnicas, las diferencias socioeconómicas que existen y los motivos de acceso y no-acceso por parte de mujeres que lo desearían.

Trabajos anteriores ponen de relieve que la proporción más baja de pacientes atendidas se suele dar en las categorías más jóvenes de 35 años (10%), seguido de pacientes de más de 42 años (11 %), y en cambio la proporción más alta de pacientes se da entre los 35 y los 39 años (63 %) (Audibert & Glass, 2015). No obstante, no todas las mujeres pueden acceder a los tratamientos con la misma facilidad. Las barreras más comunes para acceder a los tratamientos de la infertilidad son el coste económico, el marco legislativo vigente y los factores socioculturales. Según han evidenciado diversos estudios, las mujeres que conciben gracias a las TRA tienen un estatus socioeconómico más privilegiado, con mayor nivel de ingresos y educación (Harris, et al., 2016; Goisis, et al. 2020; Chambers, et al., 2013; Datta, et. al., 2016; Alon & Pinilla, 2021). Estas mujeres son también las que más posponen la entrada a la maternidad, y además las que tienen más capacidad de asumir el coste económico del tratamiento. Según algunos estudios (Präg & Mills, 2017) la aceptación cultural normativa de las TRA es un importante impulsor de estos tratamientos en Europa, más allá de las diferencias en la riqueza de los países, los aspectos demográficos o la composición religiosa.

Nos preguntamos aquí si en el caso español, en el que el acceso a la reproducción asistida está poco restringido por la legislación y, en teoría, cubierto por la sanidad pública y en el que el retraso de la maternidad es muy generalizado, también encontraremos estas diferencias en el acceso y el uso de los tratamientos de reproducción asistida (TRA).

En este trabajo analizamos los datos de la Encuesta de Fecundidad española de 2018 para analizar el auge de la demanda y uso de los TRA en España y comprender los factores que explican este auge. En concreto, se establecen estos tres objetivos:

1. Estimar la demanda real y el uso de tratamientos de reproducción asistida en España

2. Caracterizar a las mujeres que recurren a la reproducción asistida y las que por varios motivos no lo pueden hacer. También comprobar si es cierto que las mujeres con un mayor estatus socioeconómico tienen más probabilidad de someterse a los TRA.

3. Entender los motivos por los que las mujeres que reportan querer someterse a TRA no acceden a ellos, y analizar las barreras de acceso que encuentran las mujeres españolas.

En definitiva, se pretende describir la demanda actual de TRA en España y hacer una descripción a fondo del acceso a tales técnicas. Aunque sabemos que la demanda ha crecido mucho en los últimos años, hasta la publicación de la Encuesta de Fecundidad de 2018 no teníamos datos para caracterizar a las mujeres que dicen necesitar de tales técnicas, y de aquellas que se someten a ellas.

2.2. Antecedentes

2.2.1. Diversidad de Tratamientos de Reproducción Asistida

Los cambios en los deseos y comportamientos reproductivos de las mujeres españolas han sido notables en las últimas décadas, y son uno de los motores de la baja fecundidad: el deseo de familias nucleares más pequeñas y el retraso de la maternidad. Sin embargo, los factores económicos y socio-demográficos, como la inestabilidad laboral y la falta de parejas estables, son los que explican la brecha entre la fecundidad deseada y la observada (Adserá & Lozano, 2011). Además, con la postergación de la edad al primer hijo también aparecen causas de tipo biológico para entender el declive de la fertilidad, que es la capacidad humana para reproducirse.

La cantidad de países que brindan información sobre TRA ha aumentado a lo largo de los años, y se calcula que Europa tuvo la mayor cantidad de ciclos de TRA en 2017 (Zegers-Hochschild et al., 2017). Sin embargo, el acceso a los tratamientos TRA varía entre los países europeos, con tasas más altas en los países nórdicos y ciertos países de Europa occidental como Francia o España. La proporción de nacidos vivos resultantes de los tratamientos de TRA se estima comparando el número de nacimientos con el número total de nacidos vivos en cada país. Las técnicas TRA incluyen las siguientes alternativas: transferencia de embriones vía fertilización in vitro, recepción de óvulos de donantes, y tratamientos de inseminación intrauterina. La diferencia en el uso de una u otra técnica se da en parte por decisión médica, según la edad y las características de salud y fertilidad de cada mujer. En este capítulo, sin embargo, no distinguimos entre ellas ya que nuestro objetivo no es médico, sino demográfico y estudiamos el perfil de las mujeres que dicen querer someterse a técnicas de reproducción en general.

2.2.2 Factores que explican el acceso diferenciado a las TRA

Esta sección analiza los factores que explican las variaciones en el uso de las técnicas de reproducción asistidas (TRA). Comparar estudios sobre la prevalencia de TRA y la búsqueda de atención médica es aún un desafío debido a las diferencias en la confiabilidad de los datos y los criterios de medición (Fauser, 2019). Sin embargo, estudios anteriores identifican varios factores que contribuyen a las variaciones en el uso de TRA.

En primer lugar, un determinante importante es el costo económico de TRA. Los problemas de asequibilidad influyen fuertemente en el acceso a TRA, creando desigualdades en países con baja cobertura pública (McCarthy-Keith et al., 2010). Incluso en países donde el uso de TRA está más extendido, los costos y la asequibilidad siguen siendo determinantes importantes del uso. La asequibilidad a nivel individual, medida como el costo neto de un ciclo de tecnología de reproducción asistida en relación con el salario disponible promedio, muestra una fuerte asociación con un mayor uso de TRA. Los países con cobertura de seguro o subsidios públicos para TRA tienen niveles más altos de uso, pero aún pueden existir barreras socioeconómicas incluso en países con financiamiento público generoso (Goisis et al., 2020; Lazzari et al., 2022).

Las normas y creencias también juegan un papel importante en el uso de TRA. Las normas sociales sobre la reproducción, como los límites de edad normativos para tener hijos, influyen en la disponibilidad de las clínicas de reproducción (Billari et al., 2011). Las creencias sobre el estado moral de los óvulos fertilizados, el derecho a tener hijos y las consideraciones éticas de las diferentes técnicas también afectan la prevalencia en el uso de TRA (Präg & Mills, 2017). Las normas y creencias religiosas moldean aún más la aceptabilidad y la utilización de TRA en diferentes sociedades.

En último lugar, las variables demográficas, en particular la postergación de la fecundidad, están asociadas con una mayor demanda de TRA (Kocourkova et al., 2014). En sociedades donde es común posponer los primeros nacimientos, existe una mayor demanda de estas tecnologías, como es el caso de España. Sin embargo, la asociación se vuelve menos evidente cuando se controlan otras variables relacionadas con aspectos culturales y valores individuales (Präg & Mills, 2017). El aplazamiento de la maternidad también está relacionado con el uso creciente de ciertos tratamientos como la donación de ovocitos (Passet-Wittig & Bujard, 2021).

En conclusión, comprender las características, el uso y los factores que influyen en la demanda y acceso a TRA es crucial debido a su creciente importancia en la dinámica de la fertilidad. Los tratamientos TRA combate la infertilidad y el riesgo de falta de hijos permanente, lo que podría contrarrestar los efectos negativos del retraso en la maternidad en las tasas totales de fecundidad (Sobotka et al., 2008). Las brechas de accesibilidad y asequibilidad contribuyen a las desigualdades en el uso de TRA, y es más probable que las personas de nivel socioeconómico más alto utilicen estos tratamientos (Goisis et al., 2022). Para el caso español, no disponíamos hasta el momento de datos para poder evaluar las barreras de acceso a los TRA. La publicación de la Encuesta de Fecundidad de 2028 nos permite cerrar esta brecha de conocimiento.

2.2.3 El contexto español

Aunque parezca sorprendente dada la fuerte tradición católica que prohibió oficialmente los métodos anticonceptivos hasta 1978, España tiene una de las normativas más liberales en reproducción asistida del mundo (de Melo-Martín, 2019). El primer esfuerzo normativo tuvo lugar en 1988 con la aprobación de la Ley 35, que fue una de las primeras leyes a nivel mundial en regular los procedimientos de concepción asistida. La ley enfatizó principios como el consentimiento informado, la divulgación completa de los riesgos, la confidencialidad de los datos del paciente y la minimización de los embriones excedentes. De hecho, la ley no sólo permitía la investigación sobre embriones no viables, si no que puso a disposición de cualquier mujer, casada o no, a través del sistema nacional de salud la posibilidad de concebir a través de TRA hasta los 40 años de edad.

En 2003, la Ley 35 fue modificada para abordar los avances científicos y tecnológicos. La nueva ley, la Ley 45/2003, limitó el número de ovocitos a fertilizar a tres por ciclo, permitió el almacenamiento prolongado de embriones congelados e introdujo opciones para la eliminación de embriones sobrantes. También permitió la investigación de cualquier exceso de embrión, independientemente de cuándo se congeló.

En 2006 entró en vigor una nueva ley, la Ley 14/2006, que deroga las leyes anteriores. Esta ley tuvo como objetivo facilitar el acceso a personas con problemas de fertilidad. Estableció procedimientos para la prevención y tratamiento de enfermedades genéticas, prohibió la clonación reproductiva e introdujo requisitos para el uso de gametos y embriones. La ley prohibía los pagos a los donantes de gametos y embriones excepto en compensación por tiempo, esfuerzo e incomodidad. También creó registros de centros de actividad de reproducción asistida y de donantes.

Una de las características importantes del caso español es el aumento de clínicas de fertilidad de tipo privado. Los tratamientos TRA son costosos y sus resultados inciertos. En 2018, las tasas de éxito promedio en las clínicas públicas y privadas en España fueron del 8 % al 27 % por ciclo de TRA, según la edad de la paciente, y de alrededor del 37 % para los ciclos con donante de óvulos (Sociedad Española de Fertilidad, 2018) Los costos en las clínicas privadas fueron de 700 a 1000 euros por un ciclo de inseminación artificial, de 3500 a 5500 euros por un ciclo de fecundación in vitro, y hasta 9000 euros por una donación de óvulos (González-Viejo et al., 2019).

Las clínicas públicas ofrecen tratamientos gratuitos, pero, sin embargo, por lo general no incluyen las donaciones de gametos. La reducción de costes de los tratamientos TRA a través de la financiación pública a menudo se justifica por las implicaciones demográficas de la infertilidad y su fuerte impacto en la calidad de vida, no solo desde una perspectiva social sino también como fuente de depresión, ansiedad y conflicto en las relaciones (Dhalwani, et al., 2013). Sin embargo, la cobertura pública es importante no solo para brindar igualdad de acceso, sino también para reducir la carga financiera de los padres jóvenes (Chambers et al., 2014).

El sistema nacional de salud español cubre hasta tres ciclos de TRA para parejas sin hijos, hasta 40 años para mujeres y 55 para hombres (Alon, Guimon & Urbanos-Garrido, 2019). Sin embargo, los pacientes pasan alrededor de un año en promedio en las listas de espera de las clínicas públicas (García de Miguel & Salvador, 2019), lo que puede retrasar la posible solución, perjudicar los resultados del tratamiento y generar desconfianza (Castilla et al., 2019). En la práctica, alrededor del 75% de los ciclos son realizados por clínicas privadas. Estudios recientes han analizado el uso de los tratamientos TRA en España (Alon & Pinilla, 2021) y han puesto de relieve que las largas listas de espera en la sanidad pública pueden explicar porque presentan menores resultados en comparación a las clínicas privadas.

2.3 Datos y Método

Se analizan los datos de la Encuesta de Fecundidad Española (2018). Esta es una encuesta transversal que recoge información sobre dos muestras separadas de hombres y mujeres de edades entre 18 y 55 años con la finalidad de estudiar trayectorias y aspiraciones reproductivas. Por primera vez la encuesta proporciona información sobre la utilización de las técnicas de reproducción asistida. Utilizamos los datos solamente de la población femenina (N=14.556) ya que la muestra original de hombres es muy limitada (N=2.169), especialmente cuando estratificamos por cohorte de nacimiento, nivel educativo e intenciones de fecundidad y acceso a TRA. Entre las mujeres, 9.167 reportaron que por lo menos una vez han intentado de quedarse embarazadas, y 810 contestaron que para quedarse embarazadas se sometieron a TRA. Otras 481 mujeres dijeron que no se sometieron, aunque lo necesitaban.

En nuestro análisis, calculamos primero la proporción de mujeres de cada cohorte que se sometieron a TRA. Limitamos el cálculo para las cohortes de mujeres nacidas entre 1962 y 1978, porque las mujeres nacidas el año 1962 fueron la primera cohorte de las entrevistadas y las mujeres nacidas en el año 1978 ya habían prácticamente terminado su etapa reproductiva en el momento de la encuesta. Para esta parte del análisis, las generaciones más jóvenes no han sido analizadas porque tienen aún varios años de vida reproductiva por delante.

En segundo lugar, se analizan las características de las mujeres que se han sometido a TRA (N=810) y las que no lo han hecho a pesar de tener problemas para concebir (N=481). En concreto, miramos la distribución de nivel de estudios, tipo de religión y nivel de religiosidad, lugar de residencia, estado civil, tipo de unión, ingresos individuales y del hogar, y paridad. Para analizar las características de las mujeres que han utilizado TRA se realiza un análisis de regresión logística, donde la variable dependiente es el acceso a TRA, codificada como 1 si se sometieron y 0 si no se sometieron a TRA pero indicaron que tenían problemas para concebir. La variable explicativa principal es nivel de estudios categorizada en tres grupos: Secundarios obligatorios o primaria, Secundarios no obligatorios, y Universitarios. Además, se añaden controles por: (1) cohorte de nacimiento, agrupados por 1963-1967, 1968-1972, 1973-1977, menores de 1978; (2) religión: cristianos, otra religión, ninguna o no contesto; y (3) paridad: nula, cuando la mujer no tiene hijos y orden de hijos para las que sí. Dada que la encuesta es de tipo transversal, no podemos añadir información sobre estado civil e ingresos porque se corresponden con el momento de la encuesta y con el momento del tratamiento.

Finalmente, se describen y se analizan los motivos que reportaron las mujeres para no someterse a las técnicas TRA, aunque reportaron haberlo necesitado. Hemos agrupado los motivos de la siguiente manera:

Tabla 2-1. Agrupación de categorías en tres grupos y distribución de cada motivo en la Encuesta de Fecundidad 2018. Mujeres.

Motivos económicos (56%)	la Seguridad Social no me lo cubre	11,6%
	no tengo tiempo	10,0%
	mi economía no me lo permite	34,9%
Motivos salud (20%)	por problemas de salud	12,3%
	tengo un impedimento físico que me impide someterme a estos tratamientos	4,8%
	prefiero tener hijos por adopción o gestación subrogada	2,7%
Motivos emocionales (23%)	creo que me causaría mucho estrés y desgaste emocional	13,1%
	mi pareja no quiere	7,0%
	mis creencias religiosas no me lo permiten	3,5%

Fuente: elaboración propia a partir de la Encuesta de Fecundidad 2018

2.4 Resultados

En esta sección presentamos los resultados de nuestro análisis acerca de: 1) la demanda y aumento de tratamientos TRA en cada cohorte, 2) los perfiles y determinantes de las mujeres que se han sometido y las que no se han sometido a dichos tratamientos, pero tuvieron problemas para concebir, 3) los principales motivos reportados por las mujeres que no se han sometido a TRA.

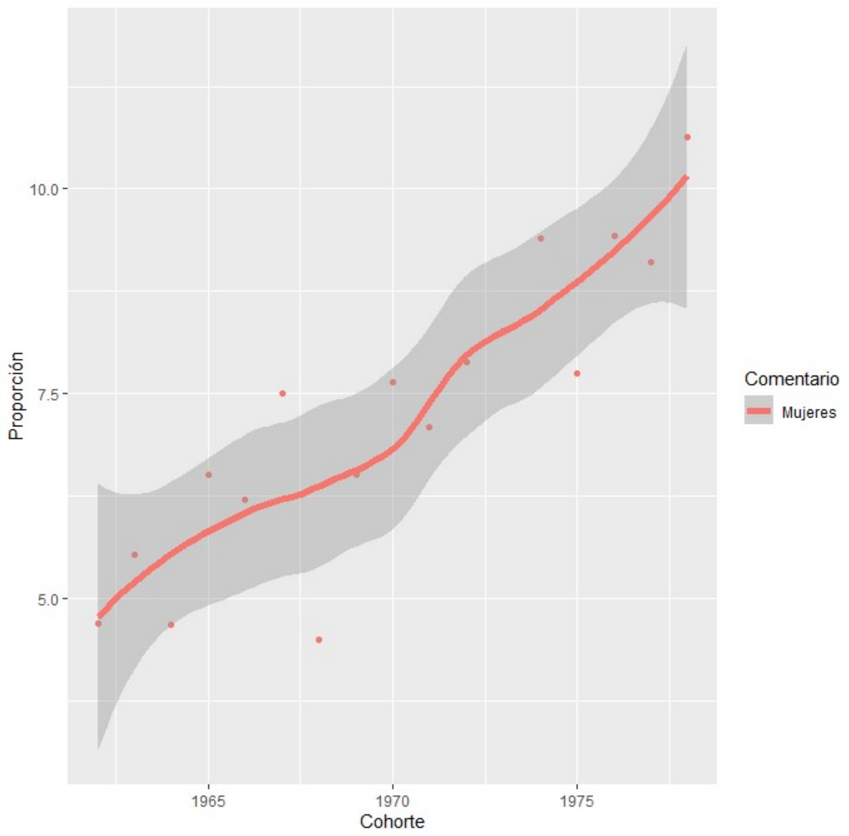
En primer lugar, nos preguntamos en qué medida el retraso de los proyectos reproductivos ha implicado un aumento de la demanda de tratamientos de reproducción asistida. Según la EF2018, el porcentaje de mujeres que se sometieron a tratamiento es de 8,8% de las que intentaban a quedarse embarazadas (5,6% de todas las mujeres). Además, un 5,2% de mujeres tuvo problemas para concebir de forma natural pero no recurrió a la asistencia médica. Como se muestra en la tabla 2-2, entre las primeras, el 52,2% lograron embarazo vía tratamientos y el 13,6% lo lograron finalmente de manera natural, mientras que el 34,1% restante nunca tuvo hijos. Del total de mujeres que no se sometieron a TRA, aunque reportaron problemas para concebir, un 59,4% nunca tuvo hijos. Entro los motivos principales para no haber podido acceder a TRA está el motivo económico (56,5%). Por lo tanto, los resultados apuntan a que no toda la demanda potencial se traduce en un uso efectivo de tratamientos. Es necesario mencionar que los motivos económicos constituyen una demanda potencial, pero no es el caso para los motivos de salud y causas emocionales ya que no representan necesariamente obstáculos evitables, como sí lo son las causas económicas.

Tabla 2-2. Demanda de las TRA en España, 2018.

	Mujeres que se sometieron a TRA	Mujeres que NO se sometieron TRA, pero reportan haberlo necesitado	
Causas de NO someterse a las TRA	-	Motivos económicos	56,50%
		Motivos de salud	19,80%
		Motivos emocionales	23,70%
Tuvieron hijos mediante TRA	52,20%	-	
Tuvieron hijos solamente de manera natural	13,60%	40,60%	
No tuvieron hijos	34,10%	59,40%	
N	***810***	***481***	

Fuente: elaboración propia a partir de la Encuesta de Fecundidad 2018

Figure 2-1. Proporción de mujeres que se sometieron a las TRA por año de nacimiento. Cohortes 1962-1978.



Fuente: elaboración propia a partir de la Encuesta de Fecundidad 2018

Como se observa en el figure 2-1, el porcentaje de mujeres que recurrieron a la reproducción asistida ha pasado del 5% para las cohortes nacidas en los años sesenta al 10% para las cohortes nacidas a finales de los setentas. Este aumento se puede deber tanto al aumento de la infertilidad debido al retraso de la edad a la maternidad, como a la mejora tecnológica de las técnicas y la cobertura de las TRA por parte del sistema público de salud.

La tabla 2-3 ofrece más elementos para caracterizar las mujeres que usan y las que no usan la reproducción asistida. Se observan diferencias en el nivel de estudios, estado civil, ingresos mensuales y la paridad entre las mujeres que entran a los tratamientos y las que no. La mayoría de las mujeres que realizan los tratamientos tienen estudios universitarios (44%), están casadas (72%) y conviven en pareja (83%). Además, la mayoría de las mujeres que se sometieron a los tratamientos tienen ingresos menores de 2000 euros. Sin embargo, las mujeres que no se sometieron a los tratamientos, la mayoría han terminado los estudios secundarios obligatorios (50%) y son solteras (30%).

La gran parte de las mujeres que utilizaron TRA no tenían hijos (90%), es decir, usan los tratamientos para la transición a la primera maternidad. De las mujeres que no se sometieron, el 56% no tenían hijos.

En relación con la religión, el grado de religiosidad y la urbanización no se encontraron diferencias relevantes entre las usuarias y no usuarias.

En la tabla 2-4 se muestran los resultados de la regresión logística en el que se presenta la probabilidad de someterse a TRA. Los resultados del primer modelo muestran que las mujeres con estudios altos y medios tienen más probabilidad de someterse a los tratamientos TRA. Los resultados ajustados (modelo 2) confirman la misma tendencia: en comparación a las mujeres con bajos niveles de estudios (primarios o secundarios obligatorios), aquellas con niveles educativos altos (universitarios) tienen una mayor probabilidad de acceder a técnicas de reproducción asistida. Esto confirma los resultados encontrados por estudios anteriores.

Las otras variables que influyen mucho en la probabilidad del uso de TRA son la cohorte y la paridad. Las mujeres nacidas antes del año 1978 (las que al momento de la encuesta tenían más de 40 años) tienen más probabilidad de someterse a TRA, porque es más difícil para ellas de concebir de manera natural. La probabilidad de someterse a TRA para las mujeres que ya tienen hijos es mucho menor de las que no tienen hijos. Con lo cual, el uso de TRA es mucho más frecuente entre mujeres con infertilidad primaria.

Tabla 2-3. Características generales de las mujeres que se sometieron y que no se sometieron a los tratamientos de reproducción asistida. España, 2018.

Variable	Uso TRA		No uso TRA		Total	
	n	%	n	%	N	%
Nivel de estudios						
Primarios y Secund. oblig.	241	29,8%	240	49,9%	481	37,3%
Secundarios no oblig.	212	26,2%	109	22,7%	321	24,9%
Universitario	357	44,1%	132	27,4%	489	37,9%
Religión						
Cristiana	535	66,0%	282	58,6%	817	63,3%
Musulmana	10	1,2%	15	3,1%	25	1,9%
Otra religión	11	1,4%	14	2,9%	25	1,9%
Ninguna o no contesta	254	31,4%	170	35,3%	424	32,8%
Religiosidad						
No religioso	268	33,1%	302	62,8%	570	44,1%
Nada o poco practicante	408	50,4%	98	20,4%	506	39,2%
Bastante o muy practicante	134	16,5%	81	16,8%	215	16,7%
Lugar de Residencia						
Urbano	423	52,2%	254	52,8%	677	52,4%
Intermedio	254	31,4%	141	29,3%	395	30,6%
Rural	133	16,4%	86	17,9%	219	17,0%
Estado civil						
Casada	582	71,9%	274	57,0%	856	66,3%
Divorciada, Sep. o Viuda	84	10,4%	63	13,1%	147	11,4%
Soltera	144	17,8%	144	29,9%	288	22,3%
Tipo de unión						
Pareja con la que convive	673	83,1%	340	70,7%	1013	78,5%
Pareja sin convivencia	41	5,1%	58	12,1%	99	7,7%
Sin pareja	96	11,9%	83	17,3%	179	13,9%
Ingresos individuales						
< 2000 euros	482	59,5%	455	94,6%	937	72,6%
> 2000 euros	328	40,5%	26	5,4%	354	27,4%
Ingresos del hogar						
< 2000 euros	527	65,1%	356	74,0%	883	68,4%
> 2000 euros	131	16,2%	42	8,7%	173	13,4%
NA's	152	18,8%	83	17,3%	235	18,2%
Cohorte quinquenal						
1963-1967	141	17,4%	73	15,2%	214	16,6%
1968-1972	165	20,4%	90	18,7%	255	19,8%
1973-1977	228	28,1%	120	24,9%	348	27,0%
Posterior a 1977	276	34,1%	198	41,2%	474	36,7%
Paridad						
Paridad 0. Primer hijo	731	90,2%	270	56,1%	1001	77,5%
Paridad 1 y más	79	9,8%	211	43,9%	290	22,5%
Total	**810**		**481**		**1291**	

Fuente: elaboración propia a partir de la Encuesta de Fecundidad 2018

Tabla 2-4. Regresión logística para el uso y no uso de las técnicas de reproducción asistida.

	Modelo 1	***Modelo 2***
(Intercept)	-0.10 (-0.31, 0.11)	0.20 (-0.13, 0.52)
Nivel de estudios. Ref. Secundarios obligatorios o primaria		
Secundarios no obligatorios	0.72*** (0.37, 1.07)	0.69*** (0.31, 1.06)
Universitario	0.98*** (0.66, 1.29)	0.91*** (0.56, 1.26)
Religión. Ref. Religión Cristiana		
Religión musulmana		-0.44 (-1.33, 0.45)
Otra religión		-0.66 (-1.65, 0.33)
Ninguna o no contesta		-0.45** (-0.77, -0,13)
Cohorte del nacimiento. Ref. Posteriores a 1977		
Cohorte 1963-1967		0.76*** (0.31, 1.21)
Cohorte 1968-1972		0.55** (0.14, 0.97)
Cohorte 1973-1977		0.51** (0.14, 0.88)
Paridad. Ref. Paridad cero		
Paridad 1 y más		-1.90*** (-2.27, -1.53)
N	1291	1291
Pseudo R2 (Cox-Shell)	0.044	0.174
*** p<0.001; ** p< 0.01; *p<0.05		

Fuente: elaboración propia a partir de la Encuesta de Fecundidad 2018

Finalmente analizamos las variables relacionadas con los motivos de no utilizar las técnicas de reproducción asistida, aunque reportan haberlo necesitado. Como se apuntó anteriormente, la causa principal de no someterse es económica. En la tabla 2.5 se puede ver que hay varias diferencias en los niveles socioeconómicos y causas principales. Un 62% de mujeres con estudios secundarios obligatorios o primarios reportaron que, la causa principal de no someterse a las TRA, fueron por motivos económicos, y un 17% que el motivo principal fue emocional. Entre las mujeres con estudios universitarios, un 50% reportaron motivos económicos y un 30% causas emocionales. Según el estado civil, el 51% de las mujeres casadas señalan causas económicas frente al 70% de las mujeres solteras. Entre las mujeres con ingresos menores de 2000 euros al mes, un 56% de ellas aluden a motivos económicos para no someterse a las TRA, y 23 % señalan causas emocionales. Al mismo tiempo, las mujeres con ingresos altos (más de 2000 euros) reportan motivos emocionales (38%) de manera más general para no someterse a las TRA. Según la edad, las mujeres de más edad reportan causas de salud (30%) mientras que las más jóvenes indican motivos económicos.

Tabla 2-5. Características de las mujeres que, a pesar de la necesidad, no se sometieron a TRA, según los motivos apuntados. España, 2018.

Variable	Causas económicas		Causas de salud		Causas emocionales	
	n	%	n	%	n	%
Nivel de estudios						
Primarios y secund. oblig.	149	62,08%	49	20,42%	42	17,50%
Secundarios no oblig.	57	52,29%	19	17,43%	33	30,28%
Universitarios	66	50,00%	27	20,45%	39	29,55%
Religión						
Cristiana	155	54,96%	71	25,18%	56	19,86%
Musulmana	7	46,67%	2	13,33%	6	40,00%
Otra religión	6	42,86%	4	28,57%	4	28,57%
Ninguna o no contesto	104	61,18%	18	10,59%	48	28,24%
Religiosidad						
No religiosa	101	52,6%	38	19,8%	53	27,6%
Nada o poco practicante	115	59,3%	41	21,1%	38	19,6%
Bastante o muy practicante	56	58,9%	16	16,8%	23	24,2%
Urbanización						
Urbano	155	61,02%	43	16,93%	56	22,05%
Intermedio	68	48,23%	34	24,11%	39	27,66%
Rural	49	56,98%	18	20,93%	19	22,09%
Estado civil						
Casada	140	51,09%	61	22,26%	73	26,64%
Divorciada, Sep. o Viuda	32	50,79%	18	28,57%	13	20,63%
Soltera	100	69,44%	16	11,11%	28	19,44%
Situación sentimental						
Pareja con la que convive	188	55,29%	70	20,59%	82	24,12%
Pareja sin convivencia	29	50,00%	14	24,14%	15	25,86%
Sin pareja	55	66,27%	11	13,25%	17	20,48%
Ingresos						
< 2000 euros	263	57,80%	88	19,34%	104	22,86%
> 2000 euros	9	34,62%	7	26,92%	10	38,46%
Ingresos de la pareja						
< 2000 euros	199	55,90%	76	21,35%	81	22,75%
> 2000 euros	18	43,90%	8	19,51%	15	36,59%
NA's	55	65,48%	11	13,10%	18	21,43%
Cohorte quinquenal						
1963-1967	32	43,84%	23	31,51%	18	24,66%
1968-1972	44	48,89%	23	25,56%	23	25,56%
1973-1977	70	58,33%	25	20,83%	25	20,83%
Posteriores a 1978	126	63,64%	24	12,12%	48	24,24%
Total	**272**		**95**		**114**	

Fuente: elaboración propia a partir de la Encuesta de Fecundidad 2018

2.5 Discusión y conclusiones

Este capítulo tiene como objetivo principal describir el perfil socioeconómico de las mujeres que se someten, o dicen necesitar, tratamientos de reproducción. La mayoría de los estudios anteriores han señalado que las mujeres que conciben vía TRA suelen ser las de nivel socioeconómico más aventajado. Sin embargo, estos estudios se han centrado en países Nórdicos y de la Europa continental, donde el porcentaje de mujeres que se someten a las TRA es inferior que en España. Para el caso español, este es uno de los primeros estudios que documenta las características socioeconómicas de las mujeres que conciben a través de tratamientos de reproducción.

Nuestro estudio estima que en España hay alrededor de 1 millón de mujeres entre 18 y 55 años que para conseguir el embarazo necesitan una ayuda médica. Sin embargo, sólo el 63% de estas mujeres han accedido a técnicas de reproducción asistida, y el motivo principal que subrayan es de índole económico. Por ello, hay una demanda potencial, ya que han indicado problemas para concebir, pero no han accedido a tratamientos médicos debido a la falta de recursos económicos. Esto podría influir en el número potencial de nacidos a través de las TRA, y que por la falta de recursos financieros no se ha logrado. Dichos resultados son similares a estudios anteriores para otros países europeos (Boivin et al., 2007).

En la línea de lo esperado, los resultados sugieren que las mujeres con el nivel educativo más bajo (Secundaria obligatoria o primaria) tienen menor acceso a TRA, confirmando los hallazgos de estudios previos. Según cohorte de nacimiento, las generaciones más jóvenes se someten a las técnicas con más frecuencia. Ello podría ser debido al retraso a la maternidad, el desarrollo de la calidad de las mismas técnicas, los cambios en las formas de familia y los avances en la legislación.

La causa más importante de no acceder a los tratamientos es la situación económica, especialmente entre las mujeres de generaciones menos jóvenes, e hipótesis más probable, a nuestro entender es, que ello se puede deber a la menor cobertura pública que tuvieron. Sin embargo, también podrían actuar factores culturales como la aceptación social de los tratamientos de reproducción. Además, los resultados de este estudio sugieren que la relación entre el acceso a TRA y su cobertura por parte de la Seguridad social no es tan sencilla como parece. No todas las mujeres menores de 40 años tienen el acceso a las clínicas públicas, ya que las listas de espera son muy largas (Alon & Pinilla, 2021), y sólo aquellas con mayores niveles económicos pueden acceder a clínicas privadas. La demanda potencial de asistencia en la reproducción no hubiera podido hacerse efectiva si no hubiera encontrado un marco favorable caracterizado por: i) la creciente aceptación social de esta opción; ii) la legislación vigente (Ley de reproducción asistida de 2006) que universaliza su acceso; iii) la importante cobertura por parte de la Sanidad pública del coste de los tratamientos.

También, a nivel descriptivo nuestros resultados apuntan que el acceso a TRA es más frecuente entre mujeres en unión que conviven con sus parejas, en comparación con mujeres solteras o sin pareja conviviente. Ello pone de manifiesto que los planes reproductivos de las españolas siguen siendo dentro de la unión estable, y con menor frecuencia mujeres sin pareja se someten a estos tratamientos como alternativa a la maternidad en solitario. Aun así, estudios anteriores han apuntado que el problema también subyace en la imposibilidad de conseguir el acceso a los tratamientos en las clínicas públicas por parte de mujeres solas y mujeres lesbianas (López, 2017). En general, las leyes que regulan las TRA afectan a una variedad de instituciones sociales: prácticas comerciales, licencias médicas, bancos de donantes, etc. Pero también tienen un efecto considerable en las personas infértiles en general y en las mujeres en particular. No obstante, rara vez se evalúan las leyes TRA para ver si promueven los intereses de las mujeres (Norwitz, Edusa, & Park, 2005). Aunque las mujeres son las únicas que se someten a tratamientos de infertilidad, la preocupación por ellas suele estar ausente de las evaluaciones de sus mecanismos reguladores. Debido a que las mujeres son las que tienen y dan a luz a los niños, la implementación y el uso de cualquier ley de TRA o regulación de tecnología reproductiva seguramente las afectará. Por lo tanto, parece necesario un análisis de cómo estas leyes podrían influir en las mujeres.

Además, este estudio presenta algunas limitaciones metodológicas importantes. Primero, las participantes de la encuesta fueran entrevistadas sólo una vez. Así que no se puede estar seguro (sobre todo, para las generaciones jóvenes) si estas mismas mujeres no se sometieron a los tratamientos más tarde del momento de la entrevista. Segundo, desde el momento de publicación de los datos, ha habido cambios relevantes en la regulación de TRA. Por ejemplo, la comunidad de Madrid cubre actualmente a mujeres hasta los 45 años vía la Seguridad Social. También hay varias diferencias en las comunidades autónomas para el acceso a las clínicas públicas, que pueden confundir a los investigadores (número de intentos, edad de la mujer, estado sentimental).

Finalmente, como ya se ha mencionado la encuesta es de corte transversal, y no longitudinal, con lo que desconocemos la situación familiar y económica de las mujeres entrevistas en el momento de someterse al tratamiento.

CAPÍTULO III. - Demographic impact of In Vitro Fertilization in Spain[3]

"Un hijo es el logro más anhelado de los padres;
la fecundación in vitro es el logro más anhelado de los médicos."
Walter P. Jeffords

Resume

In this chapter we analysed In Vitro Fertilization (IVF) data from the registry of the Spanish Society of Fertility (SEF). This registry is not complete until 2014, when it started to be mandatory, as a part of the clinics did not report until that year. Also, information on patients is very limited. Our first purpose was to estimate the number of births obtained by IVF in Spain for the period 1999-2019, correcting for non-participation. In this sense, we stressed the importance of estimating the number of pregnancies with unknown evolution and the demand for IVF by non-resident women in the country, to arrive at a correct estimate of the weight of IVF in total births. We also discuss what kind of improvements could make this registry more useful, for the purposes of demographic and social analysis, but also to be able to better measure the effectiveness of these techniques. This paper shows the limits of having only aggregated data. In the near future the SEF registry will become individual, and it is hoped that it can be even more useful in determining the impact of IVF and to what degree public demand is fulfilled.

We estimate that in year 2019 around 6.5% of births in Spain correspond to IVFs, very close to the figure for Denmark, the European country with the highest level. The proportion of deliveries lost to follow-up was high in the 2000s, over 20%, but lowered in the 2010s down to less than 10% and we estimate that in year 2019 around 35% of cycles were for women residing abroad. These estimates correlate well with what we observe from the Spanish Fertility Survey of 2018.

[3] This chapter is realized in collaboration with Daniel Devolder

3.1. Introduction

The use of in vitro fertilization (IVF) in Spain has grown at a very fast rate over the last three decades where it has a notably higher impact than in most other developed countries. Thus, in 2015 Spain was for the first time the European country where most IVF cycles were carried out, position it maintained in 2016, but lost to Russia in 2017 (according to yearly reports of the European Society of Human Reproduction and Embryology, or ESHRE, on Assisted Reproductive Techniques, or ART). Moreover, as we will show, the proportion of total births obtained by IVF was in 2017 more than three times higher in Spain than in France and the United States (according to data from the US Centers for Disease Control and Prevention, or CDC), and comparable to Denmark, the European country with the highest level registered.

In Spain, the first factor that explains this strong demand is the considerable delay in the age of first motherhood, which reached 31 years in 2018, and leads more than 40% of women of childbearing age to reach 35 years childless, at an age after which the probability of having a birth begins to drop significantly. South Korea has the highest age at first birth in the world at 31.9 years in 2018, the lowest fertility level of 0.98 children per woman this year (Statistics Korea, 2019), and is also one of the countries with the highest proportion of IVF births, with 5.8% of all births in 2017 due only to IVF births funded by state programmes (Kim, 2019). However, fertility postponement is not the only determinant, since in Italy, a country with a similar age at first childbearing than Spain, the proportion of births due to IVF was less than half the level of Spain in 2014. Other factors, such as the legal and social framework, and above all the subsidies of the health system, seem to play an important role (Kocourkova et al., 2014; Präg & Mills, 2017) to explain the strong demand for assisted reproduction in countries like Denmark, where coverage is universal for women under 40, or like Israel, where IVF is free up to 45 years of age (Birenbaum-Carmeli, 2016). Indeed, IVF with own eggs is fully subsidized in Spain for women under 40 years of age, with or without a partner, for up to three cycles and the 2006 law on Assisted Reproduction has very few restrictions, as only surrogacy is banned (Calhaz-Jorge et al., 2020).

In this context it is important to study the evolution of IVF in Spain, because it is the European country with the most important business activity in this sector, and because Spanish centres are those that respond to most of the European demand for IVF with donor eggs. In this work we found out to what extent the information collected in the

IVF registry, carried out by the Spanish Society of Fertility (SEF), is useful for social analysis, what limitations it has in this regard and how these could be improved in the future. Specifically, we want to study in this paper the effect of IVF on the birth rate. This led us to discuss in detail the degree of coverage of the registry and the quality of the data obtained. We will see that, in order to measure this effect, it is necessary to make corrections, due to shortcomings specific to the Spanish registry, but often common to all equivalent registries and which are not always known or recognized by analysts. Another important related point, but which we did not address in this study, is the difference between what we could call the medical doctor's point of view and that of the demographer: the former is interested in knowing how many births begin with an assisted reproduction treatment, while for the latter the interest is in determining the number of births that would not have occurred without the use of this technique, since some women would have had them naturally with a little more patience. In this study, and for simplicity, we will use the doctor's point of view, that is to say to count all the births due to IVF (the demographer's point of view is assumed for example by Leridon (2004).

3.2. Material and methods

In this work, we mainly used data from the Spanish registry reports for the years 1999-2019, available on the SEF website (and accompanied each year by a publication, the last being: Cuevas et al., 2020), which we complemented with data from the IVF registry of the Spanish region of Catalonia (the last report published corresponds to the data for the year 2014, and unfortunately the registry was abandoned afterwards). We have also used data from the reports of the European Society of Human Reproduction and Embryology (ESHRE) which is the European counterpart of the SEF. ESHRE centralizes data from European registries, including those of the SEF. We completed this data with information from the Belgian (Belgian Registry for Assisted Procreation - Belrap), Danish (Danish Fertility Service - DFS), Russian (Russian Association of Human Reproduction - RAHR) and United States (Center for Disease Control and Prevention - CDC) registries (see the references in the data section at the end).

National IVF registries vary in nature, with some being mandatory and others being voluntary. Many are of an aggregate type, but some are also based on individual data, which explains in part the differences in their results and quality of coverage (De Geyter et al., 2019), what we discuss below. Concerning the Spanish registry, we analysed in this paper the evolution: of its degree of coverage, of the number of cycles initiated and of the effects of IVF on the birth rate. This leads us to discuss factors usually not taken into account by ESHRE in their reports, like the under registry of births by IVF due to the incomplete follow-up of deliveries, or the existence of the "cross border reproductive care", when patients prefer to travel abroad to get access to IVF, factors whose weight is highly variables across countries.

3.3 Results

3.3.1 The registry of In Vitro Fertilization in Spain

Since 1993, the SEF has published annual reports containing the data on IVF carried out in Spain. These reports have improved notably with time, both in detail and exhaustiveness, and they incorporate data on Intra-Uterine Insemination (IUI) from 1999 onwards. From the beginning reporting was voluntary, and until 2005 less than half of the centres authorised by the Ministry of Health participated. Coverage increase afterwards and reached 92% of the authorized clinics in 2015, while the remaining 8% probably had no activity this year. Participation is compulsory, starting with treatments carried on in 2014, as the SEF registry had become the official one at the national level, and therefore the coverage of IVF, as well as of IUI, can be considered exhaustive from year 2015, as in year 2014 the data of some of the last centres to join was not included due to a lack of compliance. This registry is thus focused on IVF and IUI, and does not provide any data on other treatments like timed intercourse with ovarian stimulation (TI), for which there is very little information in Spain, when it is a common treatment in other countries (Jones, 2003; Schieve et al., 2009), while it is covered in the Belgian reports on "non-IVF" technique. In fact there is a consensus on the point that only IVF should be considered as Assisted Reproductive Techniques (ART), when both IUI and TI should be included in the wider category of Medically Assisted Reproduction (MAR) treatments: Zegers-Hochschild et al., 2017).

Another notable limitation is that information about patients is very scarce, as the approach is generally more clinical than social. Thus, the data analysed are "cycles" of IVF initiated, and the total number of patients for most treatments is not even known. As a result, it is not possible to determine exactly from the information in this registry what proportion of women have received assisted reproduction treatment, be it IVF, IUI and even less TI, nor what proportion manage to have children with the use of these techniques, because there is no follow-up of patients from cycle to cycle, unlike again, in the Belgian registry. Sociodemographic information is also very poor, age information is always provided in five-years age groups, and there is no direct indication of coverage by the public health system. Although the SEF reports include a breakdown of the numbers of IVF centres by region and public or private status, no information is given on the proportion of treatments conducted in public hospitals. However, (Castilla et al., 2009) were able to estimate the weight of public coverage in the 2002-04 period using the unpublished IVF data provided by clinics, which are later aggregated in the SEF reports: approximately 25% of the IVF were carried out by the public system in that period, and more than 95% of the egg donation took place in private clinics.

The situation in Spain contrasts with other countries, where registration is complete and information on women is more detailed. For example, Denmark, France, the Netherlands, Sweden and the United Kingdom have had a complete registry of IVF since at least 1997. Moreover, in these countries it is often possible to link the individual data in the IVF registry with other administrative and demographic sources, which makes it possible to take into account the social and medical context of the patients (as an example, see Jensen et al. 2008).

Since its inception, this registry has been compiled from information provided in an aggregate manner by each centre: each one prepares tables in a common format that it then communicates to the SEF for its annual report. The compulsory registry carried out in the Spanish region of Catalonia by FIVCAT (Bosser et al., 2009) started almost at the same time, and the collection was exhaustive. At the beginning it followed the same procedure of compiling aggregate tables for each centre, but from 2001 onwards, the information was of an individual nature, and each centre was connected to a common database, in a telematic way (for a comparison of the two registries, see Luceño et al. (2010). As mentioned above, it seems that the Catalan registry is no longer being carried out at present. The reason why is that an individualized and centralized registry of IVF is being implemented at the Spanish level, which would play a double role with the Catalan registry, although this will not be fully operational until year 2022 or 2023.

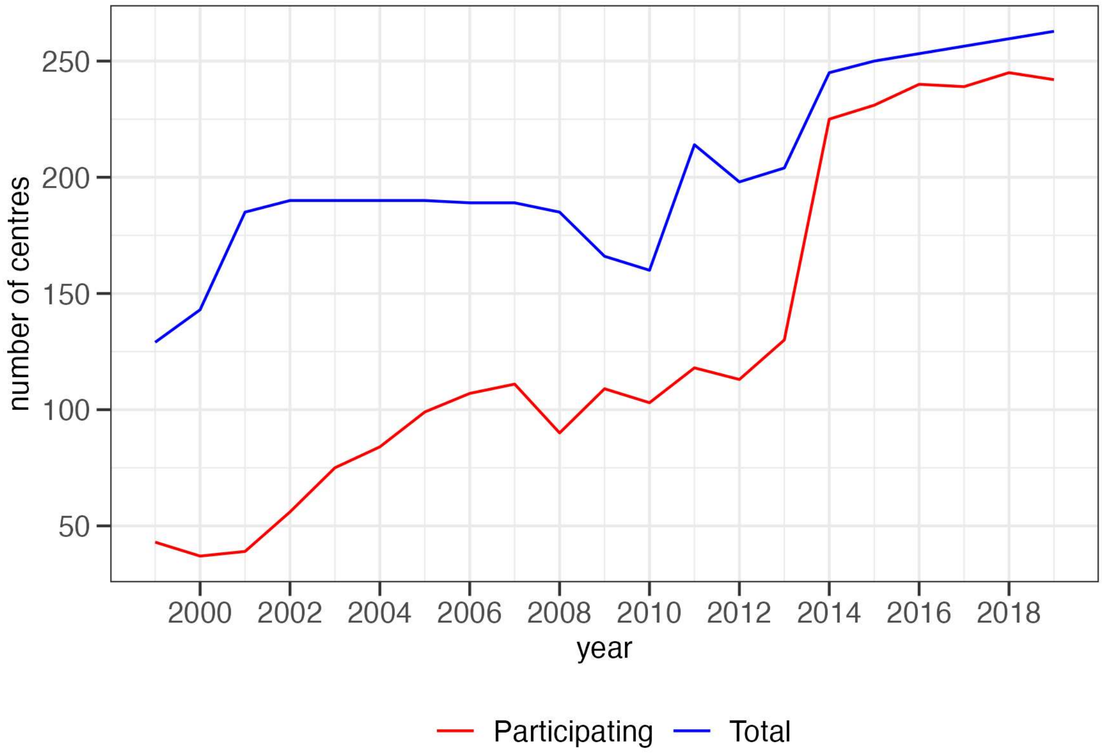
The procedure for collecting and analysing data by the SEF is longitudinal: each treatment that begins throughout the year is attempted to be followed to its end, for example, from egg collection to delivery. Therefore, the births included in each annual report refer to a period that includes the last months of the current year plus the first 9 months of the following year. This explains why reports on IVF cycles are usually published two years later, and why a not insignificant proportion of pregnancies have unknown results, if the centre that initiated the IVF cannot follow the patient until delivery. In contrast, the exploitation of the Catalan registry at the beginning was of a cross-sectional type, as described in their publications. This means that all the data collected belong to the same year, and therefore most of the births included in the annual report do not correspond to the IVF or IUI recorded for the same year. This considerably biases certain estimates, due to the strong growth in assisted reproduction, especially at the beginning of the 2000's. It is only as of 2009 that the FIVCAT reports also include a longitudinal type of exploitation like that used by the SEF, i.e., with the follow-up of each treatment until birth. However, these reports provide more complete and useful information on the patients than the Spanish one.

3.3.2 Evolution of the number of clinics in Spain

Figure 3-1 displays the evolution of the number of clinics that were authorised by the Ministry of Health to carry out IVF treatments, as well as those that voluntarily participated in the collection of data by the SEF. In general terms, the number of authorised centres remained relatively stable from 2000 to 2010 and increased steadily thereafter. Nonetheless this number decreased slightly in the years 2009 and 2010, and again in 2012 and 2013, although we do not know if this is due to the general economic situation or to an update of the data of the registry of centres by the Ministry, although the former is more likely.

Until 2013, the proportion of registered clinics reporting IVF-related activity was relatively low and gradually increased from approximately 30% to 60%. This proportion decreased in 2008, when the SEF proposed to publish detailed results of the centres, which led to the temporary withdrawal of some of them (Fuente & Requena, 2011). This publication was finally made in a very limited way, and the comparison of results between centres was ruled out, contrary to what is done, for example, by the US registry, which provides data on the effectiveness of the activity of each centre. There is a significant jump in this proportion in years 2014 and 2015, during which more than 90% of the registered clinics reported IVF cycles to the SEF, and probably the rest did not have any activity. This is due to the legal obligation for centres to report their ART treatments, beginning with the 2014 registry, although the registry is complete only starting in 2015.

Figure 3-1. Evolution of the number of centres in Spain authorized by the Ministry of Health to perform IVF, and of the number participating in the SEF registry, 1999-2019

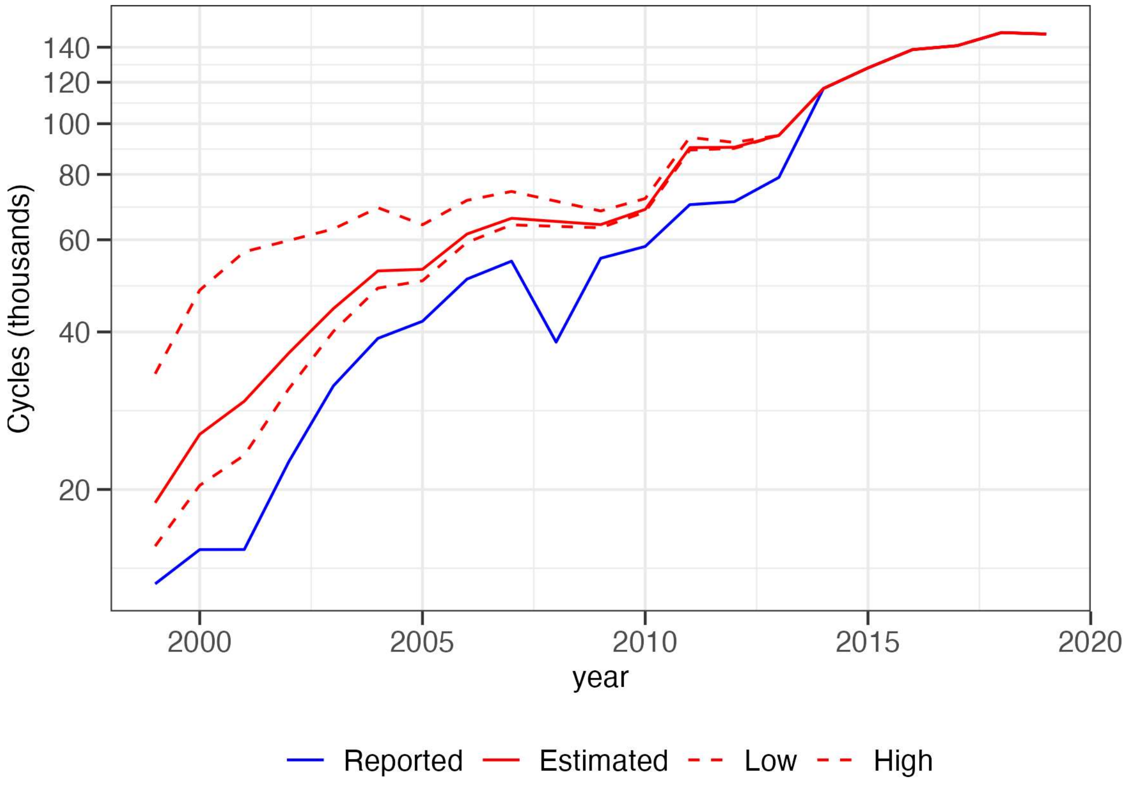


Source. Data from SEF reports. The total number of authorized centres is interpolated for the period 2016-2019, using the number of 266 centres for year 2021 reported by the Spanish Ministry of Health (http://www.cnrha.msssi.gob.es/registros/centros/home.htm).

3.3.3 Number of cycles

Figure 3-2 presents data on the number of cycles initiated by all types of IVF registered by the SEF and corrected to consider that only a part of the clinics reported. A sustained increase is observed throughout the period, with a smaller increase in the years 2008-10, probably again due to the economic crisis. During the period observed, the number of cycles increased by a factor of 8, with a faster growth until 2004, at an annual rate of 20%, which then slowed down, with an annual rate of 8% between 2004 and 2019.

Figure 3-2. Evolution of the number of IVF cycles initiated in the year indicated and corrected for non-participation, 1999-2019



Data derived from SEF reports. Logarithmic scale for the cycles. The estimated series is derived from the reported number of cycles with a correction for non-reporting of a significant proportion of centres (the relative size of clinics that do not report, compared to those that inform, varies linearly between 24% in 1999 and 45% in 2013). The dashed line curves are alternative estimates for judging of the sensitivity of the correction procedure: the lower-level curve corresponds to the hypothesis that clinics not reporting performed in year 1999 an average number of cycles equal to 10% of the number of those reporting, and the higher-level curve to a relative level in year 1999 of 86%, with a linear variation up to year 2013 with the same relative size of 45% than the main hypothesis.

The correction applied consists of trying to estimate the number of cycles performed by the clinics that did not report to the SEF, even if they have been active. One of the criterions we followed consisted of obtaining annual numbers of cycles in Spain such that the trend in time and the level of the proportion resulting from IVF births of resident women are similar to those observed for Catalonia, where the data in the registry are in principle exhaustive since at least 1999. We also rely on the evolution of the proportion of clinics participating in the registry. Thus, for example, based on the values for the years 2013 and 2014, when the greatest jump in this proportion ting occurred (from 64% to 92% of registered centres), we estimated that the clinics that began to report in 2014 carried out 45% of the average number of treatments of those that already reported in 2013.

To arrive at that estimate, we hypothesized that the two types of centres, those that reported to the SEF in the initial year and those that reported as of the final year, grew at the same rate in the period, equal to 8%, which is the approximate annual growth rate of the number of cycles in that period. To estimate the relative size of the centres that did not report at year *t*, we used the formula:

$$\frac{S_t^2}{S_t^1} = \frac{[C_{t+1}/(1+0.08) - C_t]/(N_{t+1} - N_t)}{C_t/N_t}$$

Where S_t^1 is the mean number of cycles reported by the centres in year *t*, obtained dividing the number of cycles C_t by the number of centres N_t; S_t^2 is the size in year *t* of the centres which started reporting in year *t+1*, estimated by $[C_{t+1}/(1+0.08) - C_t]/(N_{t+1} - N_t)$. Observe that in this way we project the mean size of centres which started to report in year *t+1* back to year *t*.

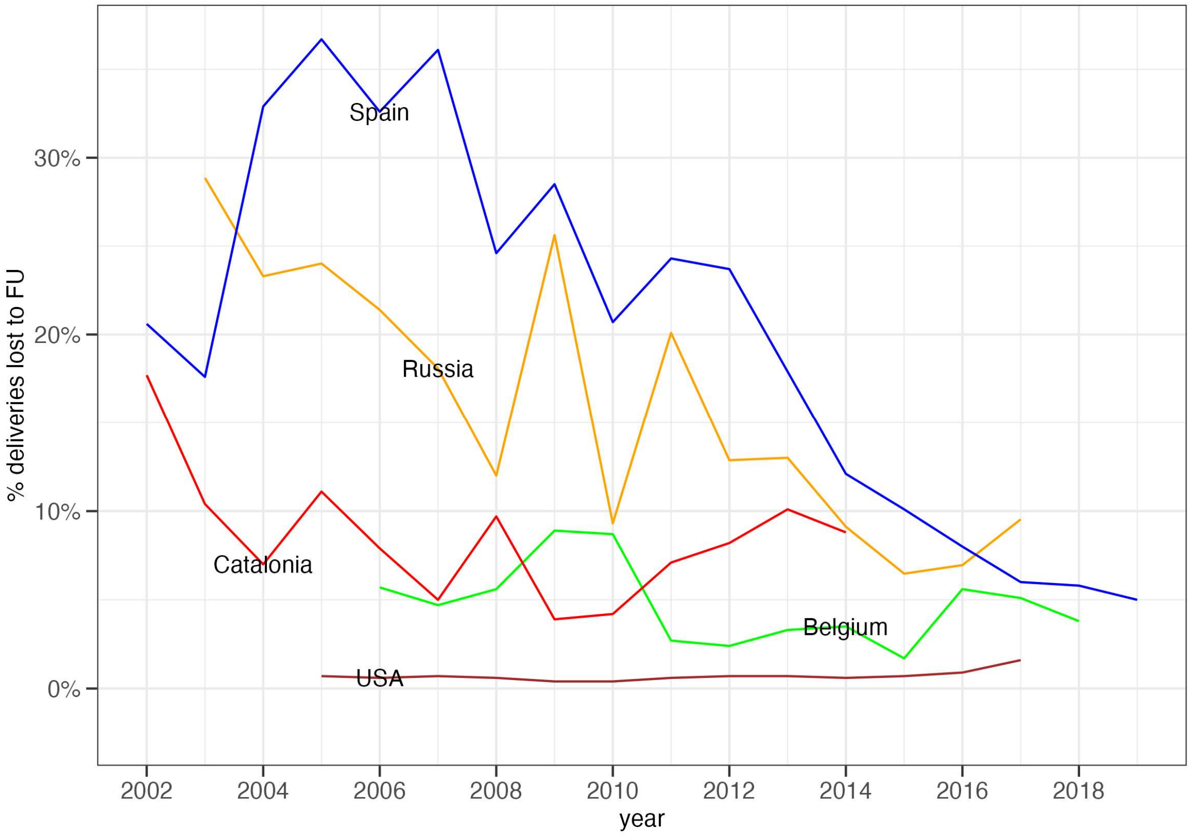
The hypothesis that we consider the most likely to reconstruct the evolution of the relative size of the IVF centres that did not report to the SEF is constructed by setting its initial value in 1999 at 24% of the size of the centres that reported. We assume that this relative size then grows in a linear fashion between 1999 and 2013, to reach the previous value of 45%.

In order to judge the sensitivity of this hypothesis, we use a set of two other initial values of this relative size, one low of 10% and one high of 86%, which provides us with two alternative series of the number of cycles, represented in figure 3-2 by the dashed line curves. For year 2008, in which there was an abrupt fall in the number of cycles recorded due to the refusal of some centres to participate, we estimated the number of cycles based on an exponential interpolation between the years 2007 and 2009.

3.3.4 Deliveries lost to follow-up

The registration of IVFs is mainly based on the monitoring of transfers of in vitro fertilised embryos to check whether they implant, i.e. give rise to a pregnancy. The time window of this follow-up is short, from one to two months. The quality of this information is usually much better than that concerning births, because women very often have their delivery in another centre, especially if they are residents of another country or region. This explains why the proportion of IVF pregnancies with unknown subsequent development is important, as shown in figure 3-3, with data for Spain and other countries. This proportion was particularly high in Spain, where it exceeded 30% during the 2000s, as well as, but to a lesser extent, in Russia, while it remained below 10% in Catalonia and Belgium and was negligible in the USA. A possible explanation for this difference is that the Spanish and the Russian registries were voluntary at that time, when it was mandatory in the three other countries. In this sense, it can be noted that the proportion of births lost to follow-up has decreased considerably in Spain since the register became exhaustive, and is now at the level of the Belgian register.

Figure 3-3. Proportion of deliveries lost to follow-up (FU), Belgium, Catalonia, Russia, Spain, USA, from 2002 to 2019



Data derived from IVF registries reports from Belgium (Belrap), Catalonia (FIVCAT), Spain (SEF), Russia (RAHR), USA (CDC). Values from Belgium and Spain are results of our internal analysis of the reports.

The problem this poses is that IVF deliveries and births will necessarily be underestimated, insofar as approximately 80% of these pregnancies with unknown evolution correspond to deliveries and births not counted by the IVF registry. It is therefore necessary to take account of this defect in the records when attempting to estimate the number of births due to IVF, and especially in international comparisons, which is not done, for example, in the ESHRE publications.

In this regard, it is important to note that estimating this proportion of "lost" births is not always easy and cannot be limited to what is directly reported by the registry but must be based on a thorough check. For example, in the case of Spain, we estimated that 36% of IVF pregnancies had an unknown evolution during 2007, when the registry only recognized a loss of 5%. Table 3-1 gives details of why this discrepancy exists, in the case of IVF cycles using fresh own eggs, which represented most treatments this year. This table shows that the annual report started with a count of all cycles, C_t, but then limited itself to the "complete" cycles, C_c, for which there was information on all phases up to delivery. Therefore, the pregnancy and delivery figures in the report did not include those for "incomplete" cycles. The report then provided two pregnancy figures, the total P_t, and those for which the results of a clinical follow-up were declared, P_c. Therefore, we have a second level of underestimation, which corresponds to pregnancies without the result of this monitoring. For these "clinical" pregnancies, information was provided about the number A of abortions and corresponding deliveries D, as well as of the "unknowns" U, which are the pregnancies without further information. But the sum of these three figures is not equal to the total number of clinical pregnancies, so there were 1,845 cases without information of any kind (that corresponds to the term N in the following formula). If we combine the four sources of underestimation of the number of births, we go from the reported figure of 5,161 to an estimate of 7,714 births per IVF with own fresh eggs, which is 49.5% higher than the number of reported births, and therefore a proportion of "lost" births equals to 33%.

As detailed in Table 3-1, we arrive at this value of 1.495 as a total multiplier of deliveries reported in the registry, which is the product of the 4 multipliers corresponding to each case of underestimation of the real number in the 2007 SEF report, as follows:

$$L = \frac{C_t}{C_c}\frac{P_t}{P_C}\left(\frac{1}{1 - U/(A + D + U)}\right)\left(\frac{1}{1 - N/P_C}\right) = \frac{D^*}{D}$$

Where L is the multiplier of births reported by the registry and D^* is the estimated total number of deliveries.

This estimate assumes that the probability of a pregnancy is the same for “complete” and “incomplete” cycles, and that pregnancies without declared clinical follow-up or those with unknown outcomes are as likely to end in delivery as pregnancies with clinical follow-up up to delivery. Note also that, if the above assumptions are valid, the proportion of “missed” births will be equal to the proportion of pregnancies lost to follow-up, which is the standard way of presenting that information.

Table 3-1. Estimate of the number of deliveries lost to follow-up, as recorded by the SEF for year 2007, for IVF from own fresh eggs

Type	Number	Multipliers of deliveries	Formula for the multipliers
C_t: Total cycles	34 499	1.049	34 499 / 32 881
C_c: Complete cycles	32 881		
P_t: Total pregnancies	9 782	1.068	9 782 / 9 158
P_C: Clinical pregnancies	9 158		
A: Abortions	1 706		
D: Deliveries	5 161		
U: Unknown evolution	446	1.065	(9 158 - 1 845) / (9 158 - 1 845 -446)
N: Not accounted for	1 845	1.252	9 158 / (9 158 - 1 845)
D^*: Estimated Deliveries	7 714	1.495	1.049 * 1.068 * 1.065 * 1.252

Data from the SEF report of 2007. Observe that the SEF reported only 446 clinical pregnancies with unknow evolution which represented 5% of the total of 9 158 in year 2007. This leads to a multiplier of pregnancies of 1.051 = 1 / (1 – 0.049) compared to our multiplier of 1.495.

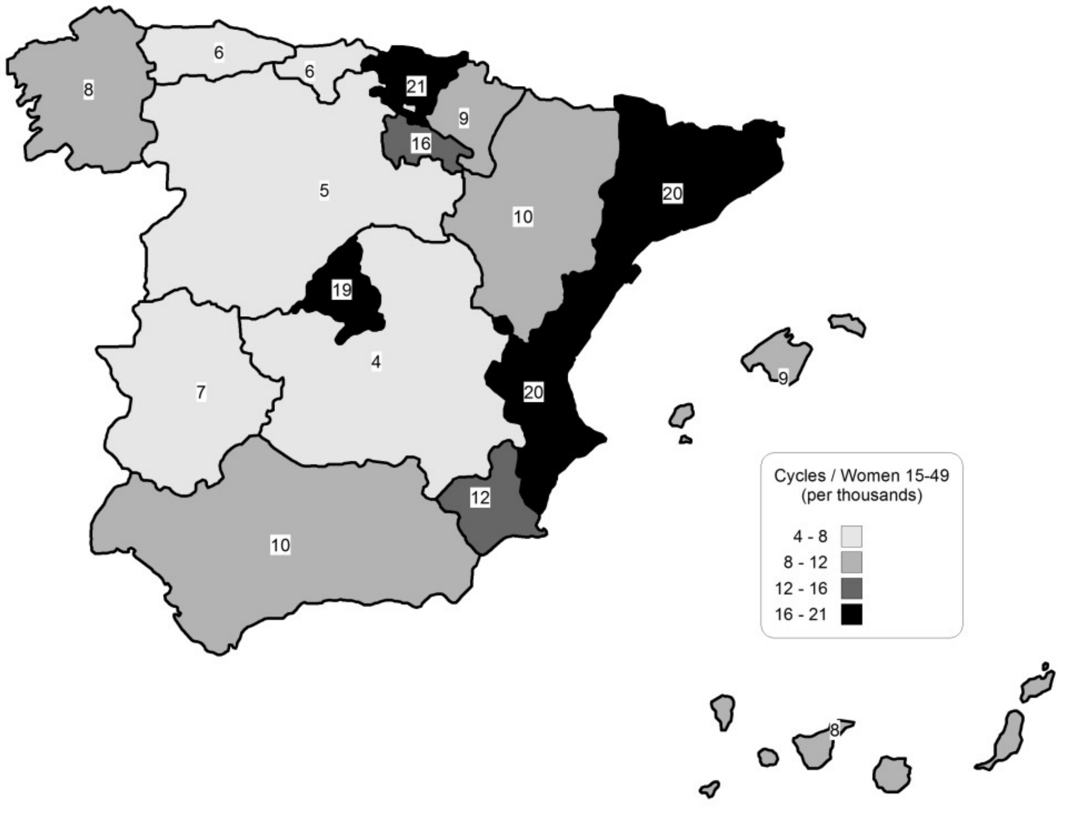
3.3.5 Differences between regions

The map in Figure 3-4 compares IVF activity by region in Spain, presenting the number of cycles carried out, divided by the number of women aged 15-49, based on data for the year 2017, during which registration was exhaustive. It is observed that there is a great disparity in the territory, with a much higher frequency in the Valencian

Community, Catalonia, Madrid, the Basque Country or La Rioja. This is probably explained by the effect of population density and economic level. In fact, clinics are preferably located in large cities and in those with the highest standard of living, since a large part of the IVFs carried out are not covered by the public health system.

But another important factor that explains these differences at a territorial level is the demand from women not resident in Spain, whose effects must be bigger in the regions with a better connection to foreign countries. These women generally move to Spain because the laws on assisted reproduction are more restrictive in other countries, especially for women without a male partner or for women who need an egg donation (Präg & Mills, 2017a).

Figure 3-4. IVF carried out during the year 2017 relative to the population of women of reproductive age (‰), for the Spanish regions



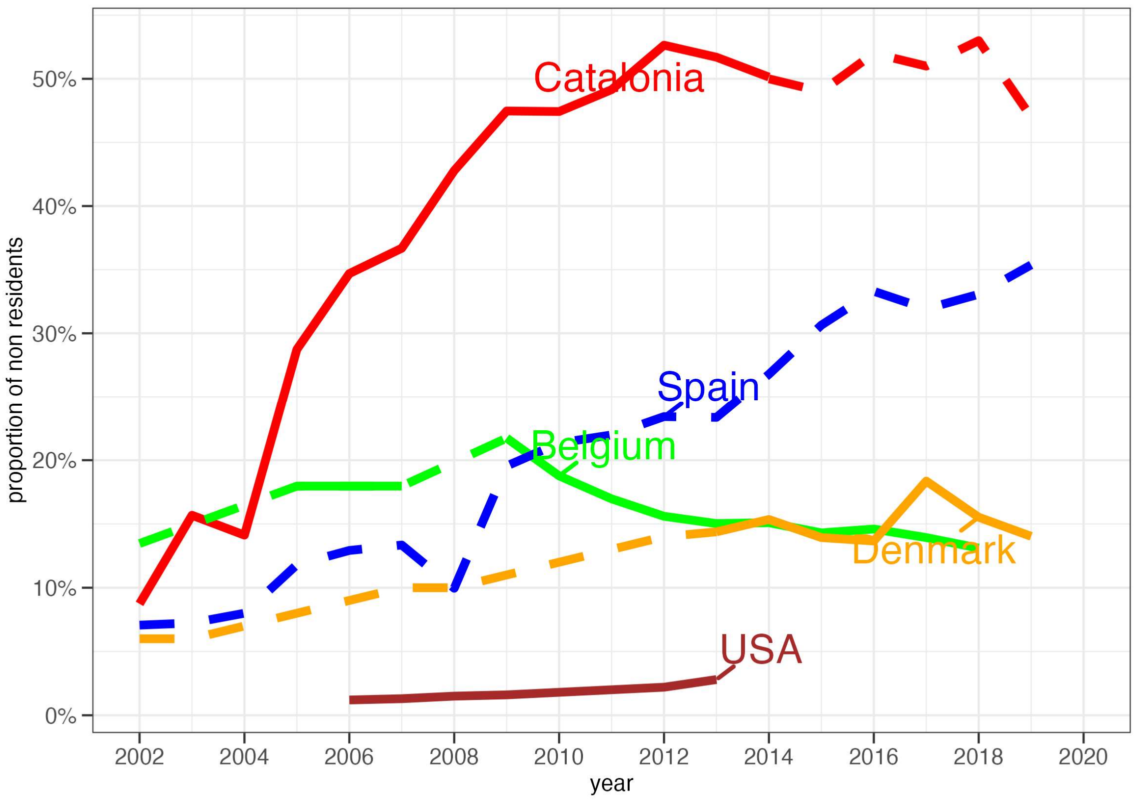
Data from the Spanish National Institute of Statistics population register and the SEF IVF report for 2017.

3.3.6 Estimating the proportion of patients residing abroad

The SEF publishes very little data on the origin or characteristics of patients undergoing IVF treatments, and these data do not appear to be accurate. Thus, the first information relating to the number of cycles for non-resident women appears in the 2014 report, from which it can be deduced that overall, 9,966 IVF cycles were reported for non-resident women out of a total of 116,688. But these data do not coincide at all with those collected in Catalonia by FIVCAT, where the report for 2014 indicated that IVF patients coming from abroad represented 48% of the total number of treatments in Catalan clinics, which would correspond to approximately 13,700 cycles, that is, much more for this region alone than the previous figure at the national level. Therefore, the proportion of non-resident patients treated in Spain is certainly much higher than indicated by the SEF, probably closer to that observed in Catalonia, especially in regions where the impact of IVF is similar, such as the Valencian region, Madrid and the Basque Country.

Figure 3-5 shows that, on the other hand, the proportion of women living abroad and treated in Catalan clinics has increased considerably since 2001 and by 2014 these patients represented half of the demand for these medical treatments, a considerably higher proportion than in two other European countries with a long tradition of receiving foreign patients, Belgium and Denmark.

Figure 3-5. Weight of Cross-Border Reproductive Care: proportion of non-residents in IVF cycles (Belgium, USA), transfers (Catalonia, Spain) or births from IVF (Denmark), from 2002 to 2019



Belgium: for the period 2005-07, proportion of non-residents in all the IVF cycles started in Belgium (Pennings et al., 2009); for the period 2010-18, proportion of non-residents in own fresh eggs cycles (Belrap reports); estimates for the rest of the time periods (dashed line). Catalonia: proportion of non-residents patients of IVF treatments, living abroad or in the rest of Spain (yearly FIVCAT reports: we assume that half of the patients whose origin is not recorded each year are resident abroad), with a projection for the period 2015-19 (dashed line). Denmark: proportion of births from IVF for residents of other countries for the period 2013-19 (Dansk Fertilitetsselskab reports) and estimates for the previous period (dashed line). Spain: estimates based on the procedure explained in the text, in the section "Estimating the proportion of patients residing abroad". USA: Levine et al. (2017).

To reconstruct the weight of the demand for IVF in Spain by non-residents, we proceed in two steps. First, we use regional data provided by the SEF registry for the period 2014-2019, when this registry was exhaustive. We base our estimates for this period on the assumption that the demand for IVF of Spanish residents was similar to the one observed in Catalonia in that period. For example (see Table 3-2), in year 2014, the demand of IVF in Catalonia by non-residents (from abroad or another Spanish region) was of half the total, which also means that the number of IVF cycles corresponding to women residing in Catalonia was 8.25 per one thousand women of fertile age. If we suppose that the demand of residents was the same in the rest of Spain (with small adjustments for less developed regions like Extremadura or the Canary Islands), we can compute by difference for each region the amount of IVF cycles that are likely to correspond to women residing abroad or in another region. Let us take the case of the Region of Valencia: in year 2014 the number of IVF cycles per one thousand women was of 16.3, from which we subtract the value of 8.25 corresponding to the demand of women resident in Catalonia, which gives us a figure of 8.05 cycles per thousand which should correspond to non-resident women. Conversely, the clinics in the Castilla-La Mancha region carried out 3.4 IVF cycles per thousand and the difference with the theoretical demand, corresponding to the Catalan level, is negative, at 4.85 per thousand. In this case, we assumed that some women from this region have moved to another region for their IVF treatment. We can then add up the excess or deficit of IVF cycles carried on by clinics in each region, which gives the total number corresponding to women living abroad, which this year represented 26.8% of the total cycles in Spain. The same calculation can then be made for the years 2015 to 2019.

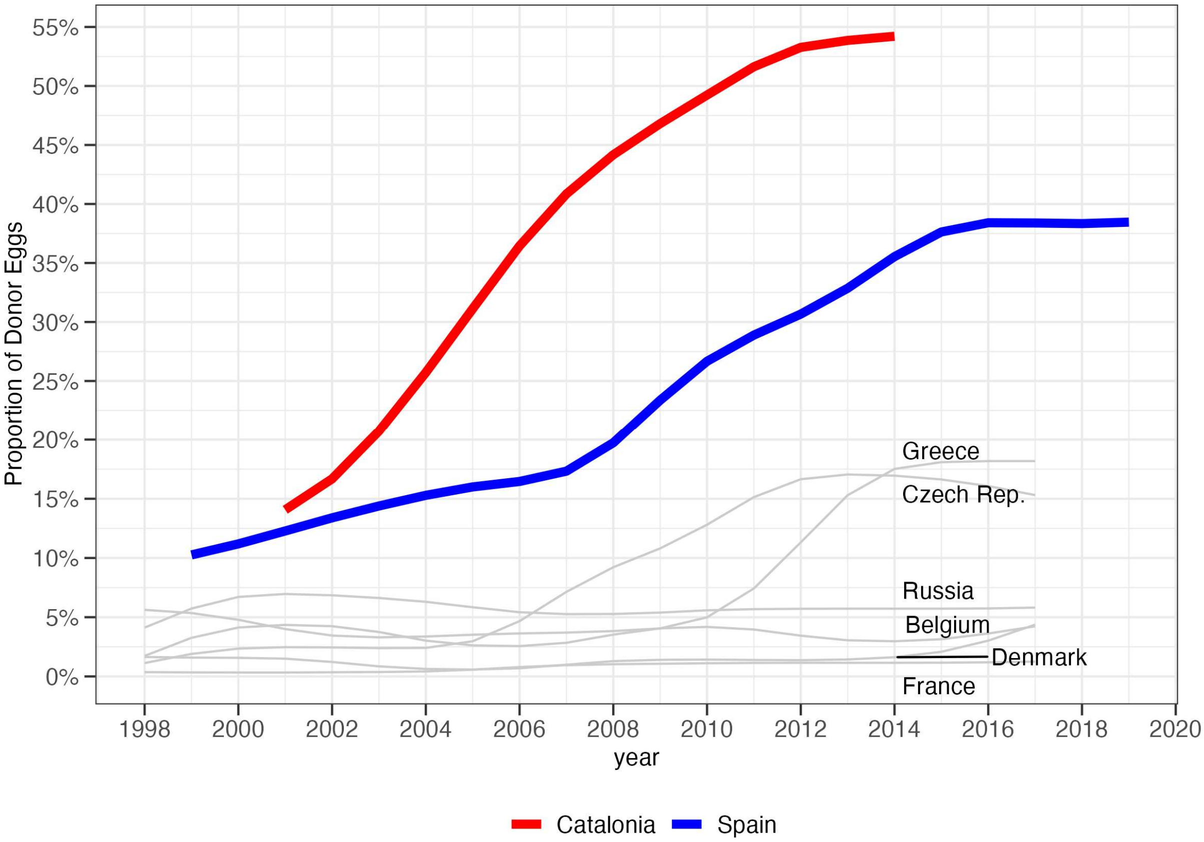
Table 3-2. Number of IVF cycles by region from 2014 to 2019 and estimates of the share of the demand of non-residents in Spain based on data for Catalonia

	Cycles per 1000 women aged 15-49						**Level relative to Catalonia**
Regions	2014	2015	2016	2017	2018	2019	
Andalusia	7.9	9.0	10.3	9.9	10.9	11.2	0.85
Aragon	9.1	9.7	8.2	9.7	10.4	10.4	0.9
Asturias	4.4	5.1	5.6	5.6	5.6	5.9	1
Balearic Islands	7.5	7.4	6.7	9.0	9.5	9.6	1
Basque Country	13.5	15.8	18.6	20.6	21.1	21.1	1
Canary Islands	7.3	7.7	8.3	8.4	8.4	8.1	0.85
Cantabria	4.5	4.6	3.7	6.1	7.7	7.2	1
Castilla-La Mancha	3.4	3.6	4.3	3.6	5.2	6.1	1
Castilla y León	4.2	4.8	5.1	5.2	4.9	5.0	1
Catalonia	16.5	17.1	19.0	19.7	21.2	18.1	1
Extremadura	5.2	7.2	6.0	7.2	7.0	8.1	0.85
Galicia	6.0	6.3	7.5	8.0	8.6	8.7	1
Region of Madrid	14.5	16.8	17.9	18.5	19.4	20.5	1
Murcia	8.9	9.5	11.4	12.4	11.0	10.4	0.9
Navarra	7.2	7.1	8.7	9.3	9.0	9.0	1
La Rioja	10.9	13.0	13.6	15.6	15.7	17.4	1
Region of Valencia	16.3	19.1	20.4	19.6	21.0	21.5	1
% Demand Non-residents in Catalonia	50.1%	49.1%	51.9%	51.4%	52.7%	47.0%	
% Demand Non-residents in Spain	26.8%	30.6%	33.3%	31.9%	33.1%	35.4%	

Data from SEF reports and Spanish Statistical Institute. These data make it possible to calculate the demand for IVF by women residing abroad: for each year the demand by women resident in Catalonia is multiplied by the standard of living coefficient in the last column, which is then subtracted from the number of cycles per thousand women in each region. This is then converted into an absolute number of cycles by multiplying this difference by the number of women of fertile age in each region, and the sum is the total number of IVF cycles of women residing abroad. Note that, starting with year 2015, the figures for the proportion of demand by non-residents in Catalonia are estimated, projecting the demand of women residing in Catalonia, assuming that the yearly increase in the number of cycles per thousand is the same than between 2013 and 2014.

The second step of this estimation procedure corresponds to the period 1999-2013 for which the SEF registry is incomplete. We start by observing that about two thirds of the demand by women residing abroad correspond to IVF cycles with donor eggs (according to the SEF reports for the period 2014-2019). Actually, the proportion of IVF treatments with donor oocytes or embryos is considerably higher in Spain and Catalonia than in the rest of Europe (figure 3-6), which is most probably a consequence of the high demand from abroad. In fact, it can be seen that in Catalonia there is a strong correspondence between the two curves for the proportion of IVF with eggs donation and for the proportion of demand from women residing abroad (comparing figures 3-5 and 3-6). These two observations form the basis of our procedure for estimating foreign demand in Spain before year 2014. First, we computed a fixed coefficient for year 2014 between the proportion of IVF cycles from women residing abroad as estimated before for Spain, and the proportion of IVF from donors' eggs, using it for estimating a series for the period 1999-2013 for the foreign demand of ART, by multiplying it each year by the proportion of IVF with egg donation. We also derived another similar series using the same coefficient, but varying each year, using similar Catalan IVFs data, multiplying these varying coefficients with the proportion of IVF with egg donation for Spain in the period 1999-2013. The final estimate for the series of the proportion of the demand of IVF by women residing abroad is then obtained by a weighting average of the preceding two estimated series, giving precedence to the series with the fixed coefficient for Spain in the last years of the 1999-2013 period and to the series with the varying coefficients for Catalonia at the start of this period.

Figure 3-6. Proportion of IVF transfers with donor eggs in Catalonia and Spain, compared with other European countries, for the period 1998-2019



Data derived from Spanish and Catalan IVF reports and from ESHRE reports for the rest of the countries (for which the proportion is computed on cycles instead of transfers). Series smoothed using Tukey's 4253H smoother.

3.4 Impact of IVF on the Birth Rate in Spain

3.4.1 *Estimated number of births per IVF.*

The cycle figures obtained above are the basis for estimating the number of births per IVF that resident women had and is used to compute its weight in the total births for Spain. These births due to IVF from women residing in Spain are estimated as follows, for each year:

$$B_t^* = B_t^{Reg} \frac{C_t^*}{C_t^{Reg}} L_t R_t$$

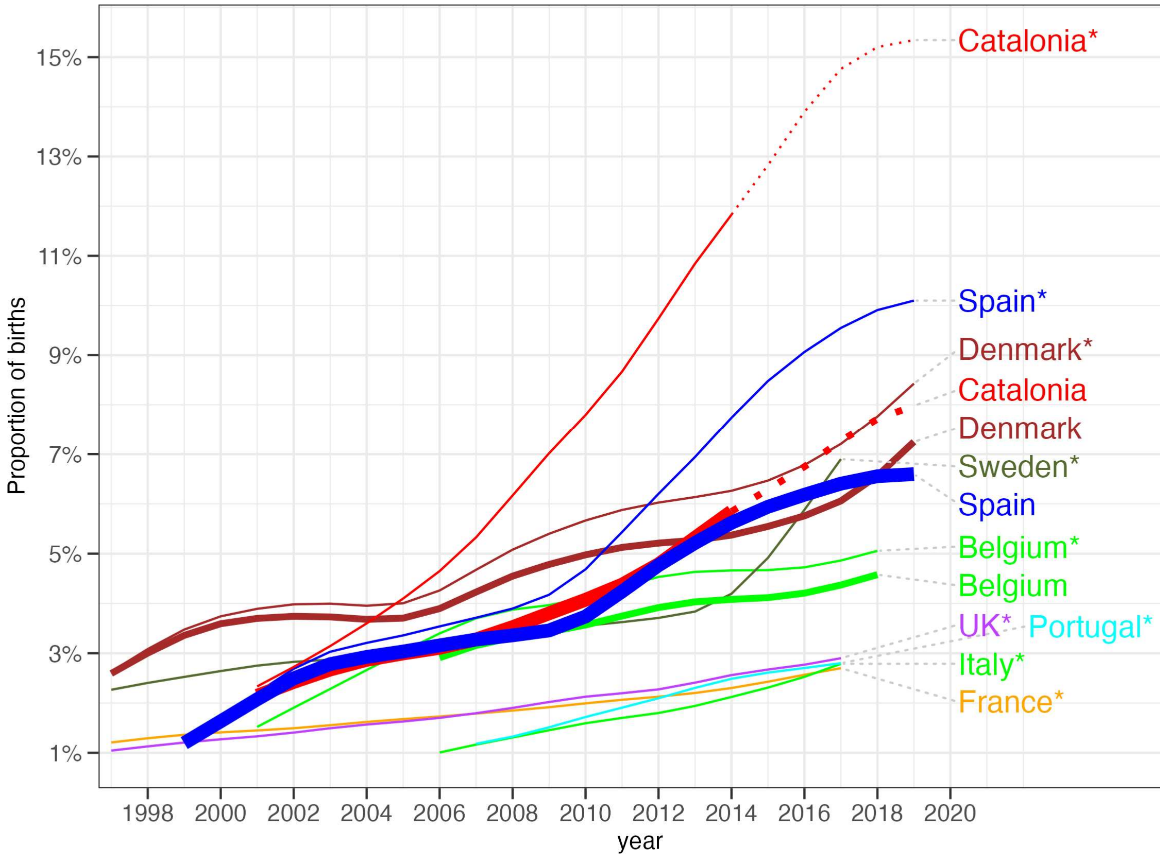
To obtain B_t^*, the estimated number of births per IVF of resident women for year t, we start from B_t^{Reg}, the number of live births obtained by IVF as reported annually in the national registry. We apply a multiplier to consider the non-participation of the centres, dividing C_t^*, the number of IVF cycles estimated previously, by C_t^{Reg}, the number of cycles reported. This number of births is then increased by multiplying it by a factor of births lost to follow-up, L_t, as calculated above. At this point we have the total number of births by IVF performed in Spanish clinics, to which we apply the proportion R_t of IVF patients residing in the country, to obtain the number of births of Spanish women started with these treatments.

Figure 3-7 presents the weight of births from IVF in the total for Spain and Catalonia, comparing with other European countries. The series are of two types: calculated from the total number of births as reported by the national IVF registries (and in this case we add an asterisk after the name of the country in the graph) and series corrected to take into account the double effect, which operates in the opposite direction, of "lost" births and of the demand for IVF by women residing abroad.

As can be seen from this chart, it is essential to consider the weight of demand for IVF by non-residents in countries where it is significant, such as Belgium, Denmark, Spain, and especially Catalonia. Thus, in Denmark IVF births in 2018 represented 8.2% of the total, but when we exclude non-residents, what is not done in ESHRE reports, the figure is down to 6.5%. The situation is more extreme in Catalonia in 2019: we estimate that births which started from an IVF in a Catalan centre represent more than 15% of the total births, but of those only 7.5% corresponds to IVF births from women who live in that region. Conversely, for countries such as France, Germany or Italy, it would be interesting to have data on patients who had to go to another country for assisted reproduction treatments, in order to have a correct estimate of the effect of IVF on their birth rate.

If we now look at the weight of IVF, net of external demand, we see that in recent years it has grown considerably in Spain, to levels higher than Belgium and close to those of Denmark, which in the last two decades has been the European country with the greatest contribution of IVF to the birth rate. But it is also remarkable to note that, in the region of Catalonia, the demographic impact of IVF is even greater than in Denmark, with a similar total population.

Figure 3-7. Proportion of total births from IVF in Spain and Catalonia compared with other European countries, 1999-2019, with and without corrections for non-resident demand and deliveries lost to follow-up



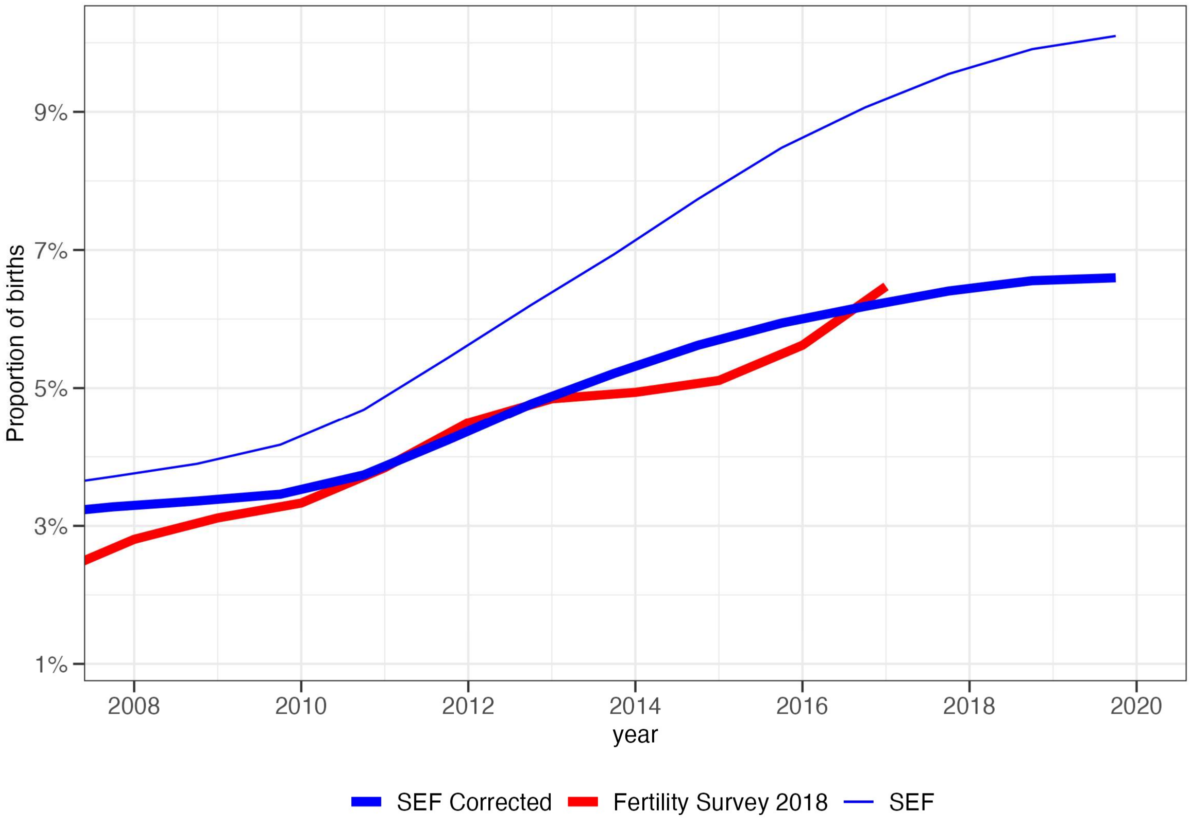
Data derived from the Spanish, Catalan, Belgian and Danish registries as well as ESHRE reports for the other countries. The series with the names of the countries followed by an asterisk correspond to the total IVF births as reported by the national registries (for Spain, with our correction for clinics which didn't report). The series for Belgium, Catalonia, Denmark and Spain plotted with thick lines correspond to births corrected to exclude non-residents women and to include births corresponding to pregnancies lost to follow-up, as explained in the text (the reports from the Danish registry do not allow us to estimate the proportion of "lost" births and therefore we have not applied the corresponding correction for this country). The series for Catalonia are extrapolated for the period 2015-19 based on the IVF cycles numbers for this region published by the SEF, equalling the numbers for both series for year 2014. Series smoothed using Tukey's 4253H smoother (Velleman, 1980).

3.4.2 *Using the Spanish Fertility Survey of year 2018 to assess the accuracy of the results*

The estimate of the number of births from the IVF register for Spain is therefore the result of three successive approximations, which correct defects of this register. Fortunately, an independent source, the Spanish Fertility Survey 2018, makes it possible to verify the goodness of the results. This survey contains questions on the use of assisted reproduction, and specifically on gestations initiated by IVF, which makes it possible to calculate the weight of this technique in the series of births reconstructed with this survey. Figure 3-8 shows the proportion of births in Spain started with an IVF after applying the three corrections detailed above, as well as the proportion as reconstructed with the Fertility Survey of 2018, both compared with the proportion computed from the "official" numbers as reported by the SEF and the ESHRE, here corrected from non-participation by some centres4. We observe that the series derived from the Spanish Survey is closer to our corrected series in recent years than the "official" one, which seems to validate our estimate than in recent years around 30 % of births initiated from an IVF treatment in Spanish clinics were from women residing abroad.

[4] Observe that we have shifted 0.75 years forward in time the two series obtained from the SEF registry to take into account that it follows cycles initiated in a calendar year and the resultant births occur 9 months later.

Figure 3-8. Proportion of total births initiated by IVF in Spain according to the Spanish Registry and the Spanish Fertility Survey for 2018



SEF Corrected: proportion of births initiated by an IVF, after correction for clinics non-participation, for births lost to follow-up and excluding births from non-resident women.

Fertility Survey 2018: own reconstruction of the births and corresponding deliveries time series by means of women birth histories from this survey, using the questions on the use of ART to determine whether the pregnancies were started by an IVF. The value of the resulting proportion for 2016 and 2017 is the average for both years and the series are later smoothed using Tukey's 4253H smoother.

SEF: series based on the number of births as reported by the SEF, but with the correction for clinics non-participation.

Note: it is important to note that in order to compare the series from the SEF and from the Fertility Survey, the dates for the IVF registry data have been shifted forward 0.75 years in time as births from cycles initiated in one calendar year occur on average 9 months later.

3.5 Discussion. Suggested improvements to the IVF register and SEF reports

Until now, the Spanish IVF register carried out by the SEF was of an aggregate type, which explains many of the shortcomings of the published reports discussed in this paper. These reports were essentially aimed at assisted reproduction professionals, which explains their focus on cycle accounting, leaving patients in a secondary position. Information on the techniques used was privileged to the detriment of other characteristics of interest, publishing for example data on cycles with innovative techniques such as 'preimplantation genetic diagnosis' without always detailing the origin of the eggs (own or donor, fresh or cryopreserved).

In the near future, this register will become individual, which could improve the annual reports, and opens up the possibility of statistical analysis, especially if the micro-data are made available to external researchers, as would be desirable and is done for example in the United Kingdom. It is hoped that the improvement in the register will also lead to a restructuring of the SEF reports. In this sense it would be desirable that these have results on the follow-up of patients, and not only on IVF cycles, for example to compute cumulative pregnancy or delivery rates. It would also be useful for both analysts and the public if the data were published mainly on the basis of 4 categories only: own or donor eggs, and for each group, cryopreservation or fresh transfer. More detailed data on the different techniques should be included in a second level of disaggregation only.

But the main advance that will allow individual-type information for analysts will be to be able to have data by simple age, and not just by large age groups as is the case now. In this sense it would be interesting to have the age of the woman treated with an IVF at the time of the transfer, but also at the time of the collection of the eggs, especially in the case that they are not her own or that there has been cryopreservation. Individual information on the patients must allow them to be monitored from cycle to cycle in order to estimate the probability of success or the time needed to obtain a live birth. This obviously requires that each patient has a unique identifier, but it is important that it could be used to link to other administrative records, which is the case for example for the IVF register in Denmark. In this respect, there is a great need for more and reliable information on patients, for example, their geographical origin (outside the region, living abroad), their family and social context, and also whether they have paid for treatment or whether it is covered by social security or a mutual fund. If this information is not directly collected in the new individual register, it could be obtained with a link to other public ones.

Current SEF reports also provide very little information about men, and it is hoped that the individual register will make it possible to know in the future whether IVF is carried out with the partner's sperm or with sperm from a donor. It would also be of interest to know more about the proportion of patients who would certainly or most probably not have had a pregnancy without IVF treatments. The only data published by the SEF refers to the "indications" for IVF treatment. In 2016, the "female factor" represented only 28.5% of these, which would seem to indicate that 71.5% of patients would have been able to have a pregnancy naturally, which is surprising. To go into details and to be able to study better the factors of success of IVF, it would be very useful, apart from counting on the age of the woman throughout the process, from the puncture to the pregnancy, to systematically collect data on the day of the embryo transfer (for example, if the blastocyst stage has been reached), on the voluntary multifetal reduction, or on the quality of the embryos. Finally, it would be very useful for patients and analysts to be able to compare the results between clinics, as the US reports of the CDC allow. This is a point of conflict, as was seen in Spain in 2008, and can be deduced from the fact that no European country yet publishes data of this type.

CAPÍTULO IV. - Standardisation and Decomposition Methods for Measuring the Effect of Assisted Reproduction on Twinning and the Birth Rate. Spain in the period 1983-2020[5]

"Ser gemelo es como nacer con un mejor amigo"

Tricia Marrapodi

Resume

Medically Assisted Reproduction (MAR) treatments have a significant impact on multiplicity in developed countries.

We estimate that MAR treatments explain 80% of the variation in twinning in Spain, compared to the figure of 55% obtained using the traditional direct standardisation method. We also show that about 8% of births in Spain in 2019 were due to MAR treatments, which is a high level by comparison with other European countries, but lower than what is reported by MAR registries, which do not properly account for the demand of patients who reside abroad.

We extend standardisation and decomposition methods to provide an accurate measure of the effect of MAR on multiple births and use a fertility survey to check the results of the estimates of the effect of these treatments on the number of births.

4.1 Introduction

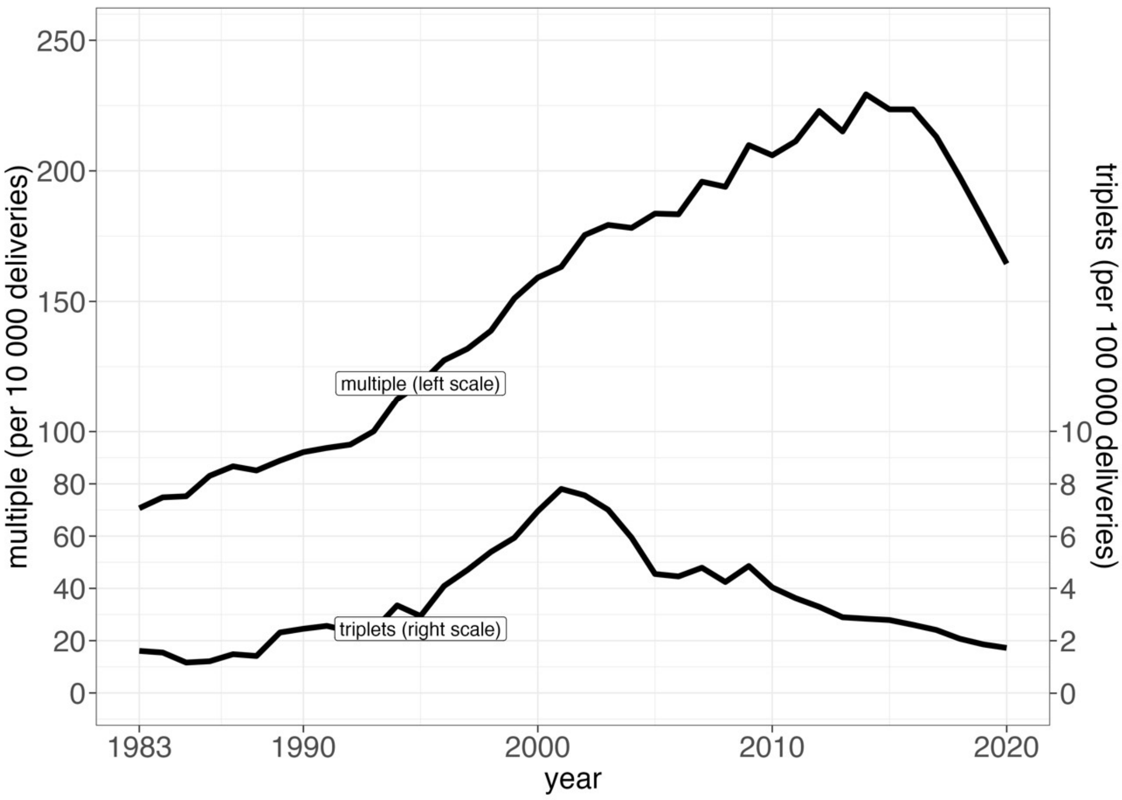
In recent decades there has been a spectacular increase in twinning worldwide, especially in developed countries (Monden et al. 2021). In the case of Spain, the proportion of multiple deliveries more than tripled between 1983 and 2014, when it reached its maximum level, from 71 deliveries with multiple births per ten thousand to 229. However, as can be seen in Figure 4-1, this proportion has decreased in recent years, to stand at 164 per ten thousand in 2020 (thus echoing a reversal that took place ten years earlier in several countries including Japan, Norway, and Sweden, as documented by Pison et al., 2015). The proportion of triplet births also increased before

[5] This chapter is realized in collaboration with Daniel Devolder

declining, but it peaked much earlier, in 2001, with recent levels similar to those of the 1980s.

The study of multiplicity and its factors has fascinated demographers, biologists, epidemiologists, and statisticians since the 19th century (see, for example, Bertillon 1874, Hellin 1895, Weinberg 1901, Strandsrov and Edelen 1946, Waterhouse 1950, and Pison and D'Addato 2006). This paper will attempt to draw on all these perspectives to construct an analysis of the factors and characteristics of the evolution of multiplicity in Spain.

Figure 4-1. Proportion of multiple and triplet deliveries in Spain in years 1983-2020



Source: authors using microdata on deliveries from the Spanish National Statistics Institute.

As we shall see, both the increase over the last three decades in the number of multiple births, and its recent decrease, are mainly due to the use of Medically Assisted Reproductive (MAR) treatments[6], which are associated with greater likelihood of a multiple pregnancy, due to the use of drugs that stimulate ovarian production in the case

[6] There is a recent consensus that the acronym ART (or Assisted Reproductive Techniques) should be used for IVF only. IUI or PI are then considered as forming part of the broader group of Medically Assisted Reproduction (MAR) treatments, which include IVF. See Zegers-Hochschild et al. (2017).

of Intra-Uterine Insemination (IUI) and the associated practice of Programmed Intercourse (PI), or to the transfer of several embryos in the treatment of infertility or sub-fertility by in vitro fertilisation (IVF), a practice that is justified by the need to improve the probability of success or, in other words, to obtain at least one live birth. In Spain, the procedure of transferring several embryos began to be restricted in the 2000s following recommendations of medical societies that were concerned by the risks for women and children of multiple pregnancies. The Spanish law on assisted reproduction of 2006 applied these recommendations by prohibiting the transfer of more than three embryos, mainly for health reasons. In the last decade, mainly due to medical recommendations, there has also been a reduction in the use of ovarian stimulation to limit the secondary effects, especially among younger women, of what is known as the ovarian hyperstimulation syndrome (van Dop 2005). This explains the decreased proportion of triple births since 2001. By contrast, the drop in total multiplicity since 2014 is due to a change in the strategies of IVF use in accordance with new recommendations from medical societies now favouring single embryo transfers (SETs). Each cycle begins with ovarian stimulation in order to obtain several eggs at the same time. These are then fertilised to obtain embryos, but only one is transferred to the woman and the rest are frozen so they can be used in case of failure to obtain a live birth. Again, the reason for these recommendations is to limit the risk of multiple pregnancy, although use of this strategy was also made possible by a considerable improvement in embryo cryopreservation techniques in recent years, through the process of vitrification (or instantaneous freezing). Progress has been so rapid that, although a recent survey (Porcu et al. 2013, for example) still considered the technique to be experimental at the time, its development into its mainstream use soon became a fact, as Rienzi et al. (2017) have indicated.

Another factor that explains the increase in multiple pregnancies is the postponement of the average age at childbearing, which in Spain, was 28.4 years in 1980, and rose to 32.3 years in 2020. In fact, the probability of a multiple pregnancy varies with the body's production of follicle-stimulating hormone (FSH), which facilitates double ovulations in a menstrual cycle and has effects that increase with age[7], as shown in

[7] Another factor is parity: multiplicity increases with parity, and is especially noticeable with 4 or more children (Bulmer, 1959; Rachootin and Olsen, 1980). This is due to the fact that the most fertile women, who are over-represented at higher parities, are generally also more likely to have multiple ovulations.

detail first by Waterhouse (1950), using Weinberg's method (1901), which we detail below.

Changes in age at childbearing and in the use of MAR interact, so it is not easy to disentangle their respective roles in the variation in multiplicity. Indeed, older women are precisely those who make most use of assisted reproductive services such as in-vitro fertilisation (IVF) and are also those who are at greater risk of multiple ovulation due to FSH hormone production.

In this chapter we attempt to:

- Determine precisely how much of the increase in twinning rates is a result of MAR and, consequently, how much is due to the greater age of mothers.

- Use these results in a second step to estimate the number of births resulting from the use of MAR in Spain, while also drawing on data from the registries of births enabled by these techniques. This will also allow us to check the quality of the data of these registries and, specifically, to assess the importance of the demand of MAR treatments by women residing abroad.

4.2 Data and methodology

4.2.1 Statistical sources used

The data used in this article have been obtained from deliveries microdata files of the Spanish National Statistical Institute (*Instituto Nacional de Estadística* -INE) for the years 1983-2020. We do not consider previous years, due to defects in classification of multiple deliveries. There were 15,851,094 deliveries in Spain in this period, including 244,765 ones with multiple births. Of these, 5,512 were triplet deliveries, 136 were quadruplet, 9 were quintuplet and 2 were sextet (stillbirths are included in these numbers).

We also use data from the registries of the Spanish Fecundity Society (*Sociedad Española de Fertilidad* - SEF) which started in 1993 to incorporate information on IVF, and on IUI cycles in 1997, but does not include data on PI (when registries from other countries, like that in Belgium, do cover this because of concerns about secondary effects of ovarian stimulation. SEF is a professional association that collects aggregated

However, the effect of this factor is very small, and completely negligible in recent times due to the reduction in fertility levels, which notably reduces the weight of large families.

data on MAR treatments by sending a questionnaire to Spanish clinics approved by the Ministry of Health. It started to release annual reports in 1999, with separate information on IVFs and IUIs, and initially covered only a minority of centres, less than 30% (Matorras et al. 2002). Participation has gradually increased to 70% in 2013 and the register, which has been official and compulsory since 2014, can be considered exhaustive from this year onwards. This register will very soon become individual and will probably be administered directly by the Ministry of Health (Devolder and Borisova (2022) - hereafter D&B – provides an analysis of the IVF data of the SEF registry). Data from the Spanish registers of MAR treatments have certain limitations and features, some specific and some common to national registers of other countries:

- These registers were incomplete until 2014, whereas the national registers of at least 10 European countries have been exhaustive since 1997 (Nygren and Andersen 2001);
- The number of births from MAR treatments is often underestimated because deliveries do not take place in assisted reproduction clinics. For example, the proportion of births "lost to follow-up" in the SEF IVF register rose to over 30% in the 2000s, although the figure has remained close to 5% in recent years. This is a problem common to the majority of national registers, as mentioned in reports of the European Society ESHRE (Wyns et al. 2021);
- Another problem is that a significant proportion of MAR treatments are carried out in another country, usually due to legal restrictions, especially for egg donation or for single women (Präg and Mills 2017). Again, this complicates international comparisons on the demographic effect of these treatments. Spain is probably the country that receives the highest numbers of women from abroad seeking MAR treatments, and unfortunately the data from the SEF registry do not seem to be very reliable: for the period 2014-19, it indicates that about 10% of IVF cycles correspond to women residing abroad. This estimate seems too low, if one compares it with, for example, the Belgian (*Belrap* reports) and Danish (*Dansk Fertilitetsselskab* reports) cases, where this proportion is reported to be around 15% in the same period. D&B estimates that the proportion of non-resident women receiving this treatment in Spain is probably closer to 35% in recent years, a figure we aim to substantiate below;

- It is important to note that the SEF procedure for collecting and analysing data is longitudinal: it is attempted to follow through to the end each treatment that begins in a certain year, for example, from egg collection to delivery. Accordingly, the births reported in each annual report refer to a period that includes the last months of the year in question plus the first 9 months of the following year, which makes adjustment necessary when computing the weight of births due to MAR (for example dividing MAR births reported for a year by births of the last trimester plus the births of the three first trimesters of next year).[8]

Finally, we use the Spanish Fertility Survey of 2018 (carried out by INE) which contains material on the use of assisted reproduction and, specifically, on gestations initiated by IVF, IUI and PI, which makes it possible to calculate the weight of this technique in the series of births reconstructed with this survey, to compare with the results obtained from the INE and SEF data.

4.2.2 Weinberg's method for determining the respective proportions of 'true' and fraternal twins

There are two types of twins, those who initially shared a single egg and known by the scientific word "monozygotic" or MZ twins for short, and those who were conceived at the same time, but from different egg and sperm cells, the "dizygotic" or DZ twins, who are similar from a genetical point of view to siblings born in different deliveries. There are few languages in which this difference gives rise to two different words for twins. Thus, in Spanish, the words "*gemelo*" and "*mellizo*" derive from the Latin word "*gemellus*", which means "born at the same time", but according to the *Diccionario de la Lengua Española de la Real Academia Española*, "*gemelos*" are of type MZ, and "*mellizos*" of type DZ. On the contrary in French the term "*jumeaux*" encompasses both, whereas in English the expression "fraternal twins" is often used for the DZ type, while "identical twins" designates MZ twins. Distinguishing between monozygotic (MZ) and dizygotic (DZ) deliveries on an individual level is a complex task and requires a DNA test that has only recently become available, or a clinical observation (Hall, 2003). However, separating the two at the population level can be done in a simple way, using the ingenious method of Bertillon (1874), which was formalised by Weinberg (1901).

[8] This adjustment is necessary for Spain and any country with a registry using the same longitudinal follow-up procedure, something that is not usually taken into account. For example, we could not find any mention of this problem in the ESHRE European reports .

This is based on the observation that multiple births with children of opposite sexes are bound to be DZ twins, and that the number of DZ twins of same sex will be the same if the sex ratio at birth of these twins is equal to 1:1. Therefore MZ deliveries can be calculated by difference:

$$\begin{cases} \mathrm{DZ} \approx 2T_{OS} \\ \mathrm{MZ} \approx T - \mathrm{DZ} \end{cases} \quad \textbf{\textit{[4.1]}}$$

where T_{OS} are deliveries of twins of opposite sex, while DZ, MZ and T are the deliveries of dizygotic twins, monozygotic twins, and their total, respectively. In fact, the calculation is somewhat more complex in practice because we exclude, in the first instance, deliveries with more than two births, and add these later to the DZ births, assuming that there are no MZ deliveries with three or more infants. Deliveries with one or more stillbirths are also included.

This formula is an approximation, as the sex ratio at birth of DZ twins is higher than 1:1, but the error in the estimate of total DZ twins is small (for a sex ratio of 1.05:1, the error will be an underestimate of 0.6‰, when in fact the sex ratio of twins is lower than for singletons, around 1.02:1 (Fellman and Eriksson 2010). This method is generally considered as statistically robust (Fellman and Eriksson 2006). It is also particularly useful for the purpose of our study, since it allows multiple births to be divided into an essentially natural component, the MZ births, and a component that is subject to the effects of MAR use, the DZ births, as will be seen below. However, Bertillon and Weinberg's basic assumption of equality between the numbers of opposite-sex and same-sex DZ twins has been criticised, since, for example, as Kanazawa et al. (2018) and Gao et al. (2019) observe, there are more same-sex DZ twins in national registries for USA, UK and China, but these are based on a classification between MZ and DZ deriving from questions the mothers are asked, which may lead to questionable results. Similarly, the assumption that the use of MAR does not change the proportion of MZ twins has been questioned and, for example, Vitthala et al. (2009) and Hviid et al. (2018) observe in two meta-analyses of IVF case studies, that embryo transfers after 5 days of in vitro culture, which is the currently recommended technique, are twice as likely to lead to MZ by comparison with a culture time of 3 days.

4.2.3 Standardisation methods for determining the role of MAR in the variations of multiplicity of births

In attempting to answer our first research question we have had to determine how much of the increased proportion of multiple deliveries is due to the use of MAR, and how much to the postponement of age at childbearing (the latter being computed either directly or as a residue). The simplest way to do this is using classical standardisation methods, which we review and extend here.

In general terms, the twinning rate (which we also call total multiplicity) is a function of the distribution of deliveries and of multiplicity, both by mother's age (as shown in Annex 1):

$$M = \sum_x m(x)d(x) \qquad \textbf{\textit{[4.2]}}$$

where M is the proportion of multiple deliveries, or total multiplicity, for a given year; $m(x)$ is multiplicity by age of mother; $d(x)$ is the proportion of deliveries by mothers of age x, with $\sum_x d(x) = 1$.

Total multiplicity M increased over time until 2014, and declined thereafter, as shown in Figure 4-1. Our purpose is to determine how much of this variation is due to the effect of MAR, taking into account, and in this case cancelling out, the effect of increasing ages at childbearing. As natural multiplicity is higher for women over 30 years of age, changes in the distribution of factors $d(x)$ can lead to variations of total multiplicity M. Conversely, the effect of the use of MAR will be reflected in increases in $m(x)$ and, therefore, the aim is to determine what part of the increase in M is explained solely by the variation in multiplicity by age. The procedure we apply next is to decompose the variation in total multiplicity, using standardisation methods, which will help to determine the respective contribution of MAR and of the postponement of age at childbearing.

The traditional method for this type of decomposition is to calculate the difference between the initial and final value of the multiplicity for the entire period studied. A first difficulty now arises since, as we have seen, its level increased from 1983 to 2014 and decreased after that. Normally, calculation of the variation would be carried out separately for the two periods of monotonic evolution, first for the period 1983-2014 and then 2014-20. But, here, we use an extension of these methods that makes it possible to obtain a decomposition for the whole period taking into account all the yearly values, instead of using only the values for the first and the last years of the period analysed. This also enables us to obtain a new series for the proportion of multiple births due to the effect of MAR alone, while eliminating the effect of variations in ages at childbearing.

4.2.4 The three methods of standardisation, direct, indirect or multiple, and their application to the measurement of the effect of MAR on the variations of the multiplicity of births

Distinguishing between effects of MAR and of ages at childbearing on the variations in total multiplicity can be achieved in three different ways using age standardisation methods, which have a long history, starting back in the eighteenth century (Keiding 1987):

- An attempt can be made to cancel out the effect of variations in ages at childbearing by using the technique of direct standardisation, starting from a standard or fixed distribution of composition factors $d(x)$, for example, by choosing those of a particular year. This is the most commonly employed method. Pison et al. (2015) and Präg et al. (2017), for example, used it to measure the contribution of MAR on the increase in multiplicity in several countries (France, Germany, Sweden, Japan, United States), using the distribution by age of deliveries at the start of the period. The problem with this procedure is that the choice of the reference year is arbitrary and, as we show below, can significantly affect the results.
- Conversely, the proportions $m(x)$ can be kept constant by applying an indirect standardisation to measure the effect of the variation of ages at childbearing, and then eliminate it from the variation of total multiplicity to obtain the effect of MAR (examples of use of this method are Elwood (1973) for Canada, Fellman and Eriksson (2005) for Danish and Finnish series starting in the nineteenth century, and Ooki (2011) for Japan). Here, unlike direct standardisation, the choice of a standard is not arbitrary, as it makes sense to use the proportions $m(x)$ of a period previous to the diffusion of MAR, when the multiplicity by age was still somehow of a "natural" type.
- Finally, a third, more complete and, in principle, improved method is that of multiple standardisation, or of the decomposition of changes in total multiplicity in terms of the variation of its two factors. This method is an improvement on the

preceding two simple standardisation methods since it is not necessary to choose any specific year as standard, or to decide between direct and indirect standardisation, since multiple standardisation is a combination of both. In this regard, we apply Kitagawa's classical method of decomposing the variation of a rate into factors, when the population is distributed by a single characteristic such as age, but with extensions that improve it and allow mitigation of its main limitations: the use of only two observations or data points to calculate the decomposition, thus discarding intermediate values; and the question of how to deal with the problem of an inverse evolution of the factors (both points discussed in Devolder, 2018).

4.2.5 Complementarity of direct and indirect standardisation

It is interesting to note that, in the context of calculating the variation of a rate, or of a proportion as is the case of total multiplicity, there is a symmetry or equivalence between the use of the two simple standardisation methods. Indeed, as Kitagawa (1955) showed, for a variation of the total multiplicity between year 1 and 2, we have:

$$\Delta M = M_2 - M_1 = \Delta M^{Dir_1} + \Delta M^{Ind_2} = \Delta M^{Dir_2} + \Delta M^{Ind_1} \qquad \textbf{\textit{[4.3]}}$$

where ΔM^{Dir_i} is the change in multiplicity measured with a direct standardisation, using the proportions of deliveries by age $d(x)$ fixed at year i, and ΔM^{Ind_i} is the variation measured with an indirect standardisation using the multiplicity by age $m(x)$ of year i. For example, for $\Delta M^{Dir_1} = M_2^{Dir_1} - M_1^{Dir_1}$ the standard corresponds to the proportions of deliveries by age of year 1, and we have for year 2:

$$M_2^{Dir_1} = \sum_x m(x,2)d(x,1)$$

Where $m(x,2)$ is the proportion of multiple births for age x in year 2 and $d(x,1)$ is the proportion of deliveries at age x in year 1, used as standard.

In other words, when it is the variation rather than the absolute value that is of interest, the two traditional standardisation methods are complementary. Hence, when a direct standardisation is carried out by keeping the age composition $d(x)$ fixed at its initial value, which is the most commonly used method, the result in terms of variation over time will be symmetrical, as per formula [4.3], to that obtained from an indirect standardisation, but using the multiplicity by age $m(x)$ of the end of the period. But, as mentioned above, it makes more sense to use as a standard the multiplicity per age of the initial year, before the dissemination of MAR, which is equivalent, as shown by formula [4.3], to a direct standardisation based on the age distribution of deliveries at the end of the period. In this case, the effect of MAR would be measured by subtracting the effect of the change in ages at childbearing from the change in total multiplicity:

$$\text{MAR Effect} = \Delta M - \Delta M^{Ind_1} = \Delta M^{Dir_2}$$

As the choice of the reference year is arbitrary for direct standardisation, but not for indirect standardisation, it would be more logical, paradoxical as it may seem, to use the age distribution of deliveries of the final year, instead of the first year as it is customary, if we want to measure the role of MAR in the variation of total multiplicity when applying direct standardisation.

4.2.6 Extending Kitagawa's decomposition method. Using all the data points of the series

As we have just seen, when analysing variations in the multiplicity of births, choosing one of the two simple standardisation methods over the other makes no difference and, moreover, the selection of a specific year as a standard is arbitrary for the direct method, which can, as we describe below, significantly affect the results. The contribution of Kitagawa (1955) was to show that there is a better solution that also leads to a univocal result. When applied to our problem, it makes it possible to obtain the decomposition of variation over time of total multiplicity in terms of the sum of the effects of the changes in two types of behaviours, those associated with the use of MAR, and those related to the postponement in the ages at childbearing, from the following formula (as detailed in Annex 1):

$$\Delta M = \sum_x \Delta m(x)\overline{d(x)} + \sum_x \Delta d(x)\overline{m(x)} \qquad \textbf{\textit{[4.3]}}$$

The first summation measures the effect of the change in multiplicity by age, represented by the terms $\Delta m(x)$, and the second is the composition by age effect, due to the change in the ages at childbearing. ΔM, $\Delta m(x)$ and $\Delta d(x)$ are, respectively, the variation during the period of study of total multiplicity, age multiplicity, and age composition of deliveries, and $\overline{m(x)}$ y $\overline{d(x)}$ are respectively the average value in the period of variation of the multiplicity by age and of the age distribution of deliveries, calculated for example by: $\overline{m(x)} = (m_2 + m_1)/2$. These mean values play the role of standardisation factors, of an indirect type when calculating the means of the $m(x)$, and of a direct type when computing the means of the $d(x)$. Hence the expression "multiple standardisation".

Kitagawa (1955) calculated the mean values and their differences by taking the initial and final values for the period analysed. This can be problematic if the period is long because it leads to an overlooking of intermediate observed values and also to the implicit assumption that the evolution of factors is linear in the period. In order to lessen the effects of these two problems, we extend her method, introducing an improvement that consists in performing the calculation annually and then accumulating the results to obtain the total decomposition. For example, for a period between years *0* and *t*, we proceed with a sum of annual changes:

$$\Delta M = M_t - M_0 = \sum_{i=1}^{i=t} (M_i - M_{i-1}) = \sum_{i=1}^{i=t} \Delta M_i$$

The decomposition of each intermediate variation ΔM_i is then obtained applying formula [4.3], and the total effect of each of our two factors is obtained by adding up their yearly components:

$$\Delta M = \sum_{i=1}^{i=t} \sum_{x} \Delta m_i(x) \overline{d_i(x)} + \sum_{i=1}^{i=t} \sum_{x} \Delta d_i(x) \overline{m_i(x)} \qquad \textit{[4.4]}$$

Again, the left-hand term corresponds to the effects of MAR use and the right-hand term measures the effects of variation in ages at childbearing.

The improvement of Kitagawa's method applied in formula [4.4] uses a logic similar to the decomposition method of Horiuchi et al. (2008), the main difference being that, in the latter, the intermediate values would be interpolated in t steps between years *0* and *t*, whereas we use the $t - 1$ intermediate yearly observed values (although Horiuchi et al. mention that using intermediate observed values is a valid alternative to their general method based on interpolation). If one uses a linear interpolation, the results of the methods of Horiuchi et al. and of Kitagawa will be identical, as can easily be shown (see annex 1). Using observed values instead of interpolated ones not only improves the measurement, but also turns out to be important when the aim is to compute the relative contribution of factors in explaining the variation in time of total multiplicity, as we now show.

4.2.7 Computing the relative contribution of factors

If one wants to measure the relative contribution of MAR to the variation in total multiplicity, one might be tempted to divide all the terms in formula [4.4] by the absolute increase ΔM, but this could lead to distorted or even incongruous results. Indeed, this formula uses yearly data which are normally variable in the short term and therefore show changes in sign. Ignoring these variations would give the same result as interpolating the yearly values of $m(x)$ and $d(x)$ between years *0* and t, which is the general solution proposed by Horiuchi et al. (2008). Another problem arises if the factors in the decomposition have an evolution in time of opposite sign. For example, in the very simple case of a sum of two terms and its variation: $\Delta a = \Delta b + \Delta c$, if $\Delta b = 7$ and $\Delta c = -6$, if we divide these two terms by the total variation $\Delta a = 1$, we will then obtain a result close to the absurd, saying that b "explains" 700% of the change in a while c "explains" minus 600%, and the degree of absurdity will increase if the variations of the two factors b and c nearly compensate each other, resulting in $\Delta a \to 0$. Another issue is the usual practice, when applying a decomposition method to a time series with ups and downs, of dividing it into several sub-periods. Thus, in the case of the evolution of multiplicity in Spain as represented in Figure 4-1, the usual approach would be to consider separately two sub-periods, from 1983 to 2014 and from 2014 to 2020, to maximise the total variation to be explained, and thus complicating the analysis.

In order first to take into account short-term variations, second so as to avoid obtaining absurd results in the case of an inverse evolution of the contributing factors and, finally, to be able to consider the data for the whole period without being forced to use various sub-periods, we introduce another extension to Kitagawa's method, this time adapted to the problem of measurement of the share of factors in the decomposition of the variation of a rate or a proportion. We therefore propose to modify formula [4.4] by taking the absolute value of annual changes:

$$\mathrm{PVar}(M) = \sum_{i=1}^{i=t} \left| \sum_x \Delta m_i(x) \overline{d_i(x)} \right| + \sum_{i=1}^{i=t} \left| \sum_x \Delta d_i(x) \overline{m_i(x)} \right| \qquad \textbf{\textit{[4.5]}}$$

$\mathrm{PVar}(M)$ corresponds to what could be called the "variation potential" of total multiplicity M and the contribution of the factors will be obtained by dividing each of them by this potential. It is important to note that we take the absolute values of the annual summations and not those of the elementary terms $\Delta m_i(x)$ and $\Delta d_i(x)$, as the latter correspond to an age distribution for which $\sum_x d_i(x) = 1$, and therefore when ages at childbearing increase, the proportions after the mean age, will typically rise, and those at younger ages will then fall automatically, which will lead to overestimation of the age composition effect.

In order to understand the benefit of using absolute values (a more general discussion is presented by Ellenberg, 2014, chapter 5), we can return to our previous simplified example for which the sum $|\Delta b| + |\Delta c|$ is now 13, and the contribution of b to the variation of a will then be $\frac{|\Delta b|}{|\Delta b|+|\Delta c|} \approx 54\%$ and that of c will be $\frac{|\Delta c|}{|\Delta b|+|\Delta c|} \approx 46\%$. This procedure is similar to a decomposition of the variance computed from absolute values of the variations, and not of their square as is usually done (Yitzhaki, 2003).

4.2.8 Obtaining a series of total multiplicity free of the variations in ages at childbearing

The previous methodological excursion brings us back to our starting point, the search for a series of total multiplicity of deliveries that considers only the effects of the use of MAR. To obtain such a series, we again start from formula [4.4] and eliminate the terms corresponding to variations in the proportions of deliveries by age, which are due to the variations of the age at childbearing. The series sought will then correspond to the following formula, calculated from year *0*:

$$ {}_tM_0^{MS} = \sum_{i=1}^{i=t} \sum_x \Delta m_i(x) \overline{d_i(x)} \qquad \textbf{\textit{[4.6]}} $$

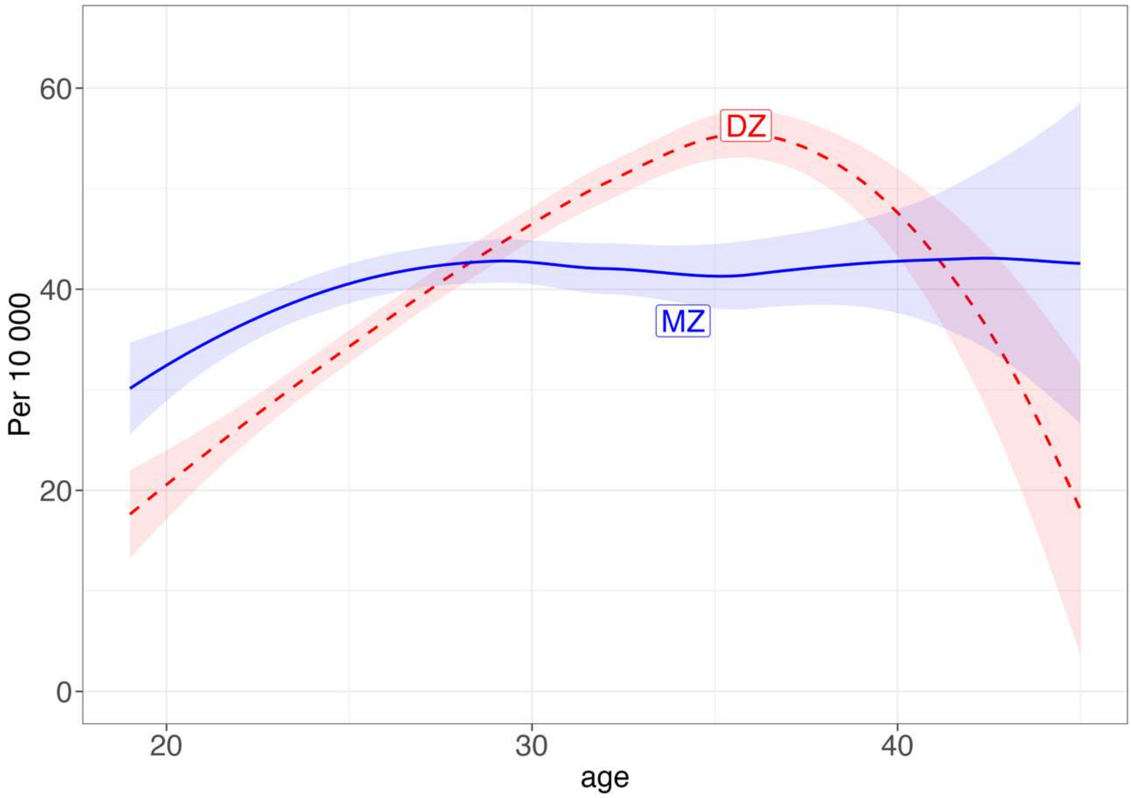
The resulting series ${}_tM_0^{MS}$ will measure the increase in multiplicity due to the use of MAR between year *0* and *t*, with MS meaning “Multiple Standardisation”. If the initial year 0 is chosen from a period before the introduction of these techniques, then ${}_tM_0^{MS}$ will be the proportion of deliveries which are multiple and due to MAR in year *t*.

4.3 Results

4.3.1 Results of Weinberg's method: MZ and DZ twins

We applied Weinberg's method to estimate the proportions of monozygotic and dizygotic "gemellus" from Spanish data for the period 1983-2020.

Figure 4-2. Proportion of MZ and DZ deliveries by age before the diffusion of MAR: average level for the period 1983-87 (in per ten thousand of total deliveries)



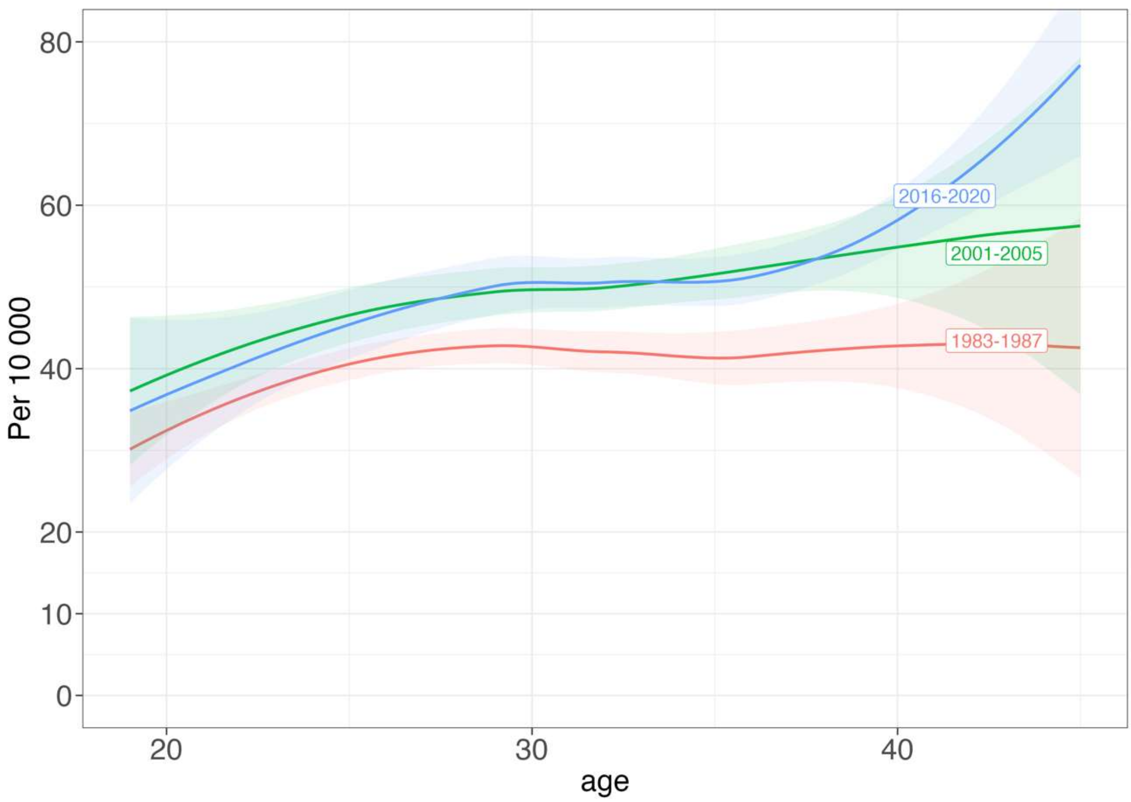
Source: authors based on deliveries microdata from the Spanish National Statistics Institute (INE). MZ and DZ twin series are computed using Weinberg's Differential method. Both series are smoothed with the Loess algorithm (Cleveland & Grosse, 1991) using the numbers of MZ or DZ twin deliveries by age for the five-year period as weights, which allows computing a 95% confidence interval for the fitted curve (the region where 95% of the fitted curves obtained with similar sets of data would be found). Data at ages 19 and 45 correspond to deliveries at age 19 and under, and age 45 and over respectively.

In the following, we will assume that the effect of MAR on multiplicity was negligible in Spain until the end of the 1980s, as the first IVF was practised in this country in 1984 and the first documented use of ovarian stimulation at the worldwide level also only started in that decade (López-Moratalla, 2012). Monitoring of MAR in Spain started only in 1999, but data for the USA, which had one of the first registries, show that the number of deliveries started from IVFs was still below 500 in the years between 1985 and 1986 (Hartz, 1988).

Figure 4-2 shows that, for the period before the diffusion of MAR, the proportion of monozygotic twins varied little by age, above 30 deliveries per 10 000, and around 40 from the age of 25 upwards. These levels correspond to what is generally observed for all human populations, although this proportion rose slightly during the 20th century in

European populations, from 30 to 40 deliveries per 10 000 (Murphy & Hey 1997), probably due to the use of the contraceptive pill (Bressers et al. 1987). The near constancy by age, as well as the similarity with commonly observed levels, validates Weinberg's method, as applied to Spanish data. Conversely, the possibility of having DZ twins varied markedly by age in this period, with a maximum value around 36 years at twice the level at 23 or 43 years, an age pattern that again corresponds to what is generally observed (Waterhouse, 1950). By contrast to MZ twins, the overall proportion of DZ twins is highly variable across human populations, with figures that are much higher in Africa and lower in Asia, especially in Japan. In this regard, the level in Spain before the diffusion of MAR was low by comparison with other European countries, with values that were, nonetheless, similar to those for Italy in the same period (Bortolus et al., 1999).

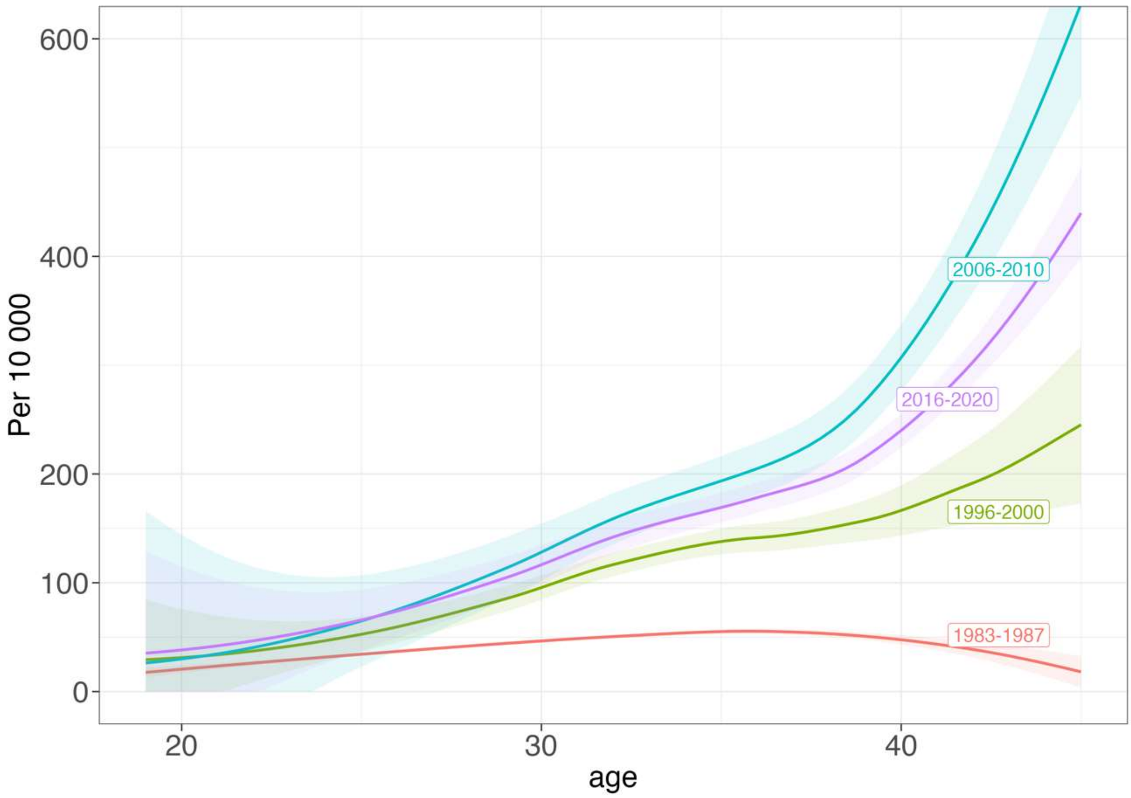
Figure 4-3. Proportion of MZ twins by age before and after introduction of MAR (in per ten thousand of total deliveries). Five-year averages for three periods



Source: authors based on deliveries microdata from the Spanish National Statistics Institute (INE). MZ twin series are computed using Weinberg's Differential method and smoothed with the Loess algorithm using the numbers of MZ twin deliveries by age for each five-year period as weights, which allows computing a 95% confidence interval for the fitted curves. Data at age 19 and 45 correspond to deliveries at ages of 19 and under and ages of 45 and over, respectively.

Figure 4-3 reveals that the use of MAR has led to an increase in the proportion of MZ twins of the order of 25% up to the age of 40 years, with a doubling of the likelihood at 45 years, confirming clinical observations reported by the authors cited above. But this increase is considerably higher for DZ twins, as shown by with a likelihood 3 to 4 times higher between 30 and 40 years of age, and up to 20 times at 45 years of age. However, the probability of having DZ twins has decreased in the more recent period, especially after the age of 40, which explains the decline in total multiplicity. It is also important to observe that the age pattern of DZ multiplicity changed dramatically as a consequence of MAR use, amplifying the effects of the postponement of childbearing ages on total multiplicity.

Figure 4-4. Proportion of DZ twins by age before and after introduction of MAR (in per ten thousand of total deliveries). Five-year averages for four periods



Source: authors based on deliveries microdata from the Spanish National Statistics Institute (INE). DZ twin series are computed using Weinberg's Differential Rule and smoothed with the Loess algorithm using the numbers of DZ twin deliveries by age for each five-year period as weights, which allows computing a 95% confidence interval for the fitted curves. Data at the ages of 19 and 45 correspond to deliveries at the ages of 19 and under, and of 45 and over, respectively.

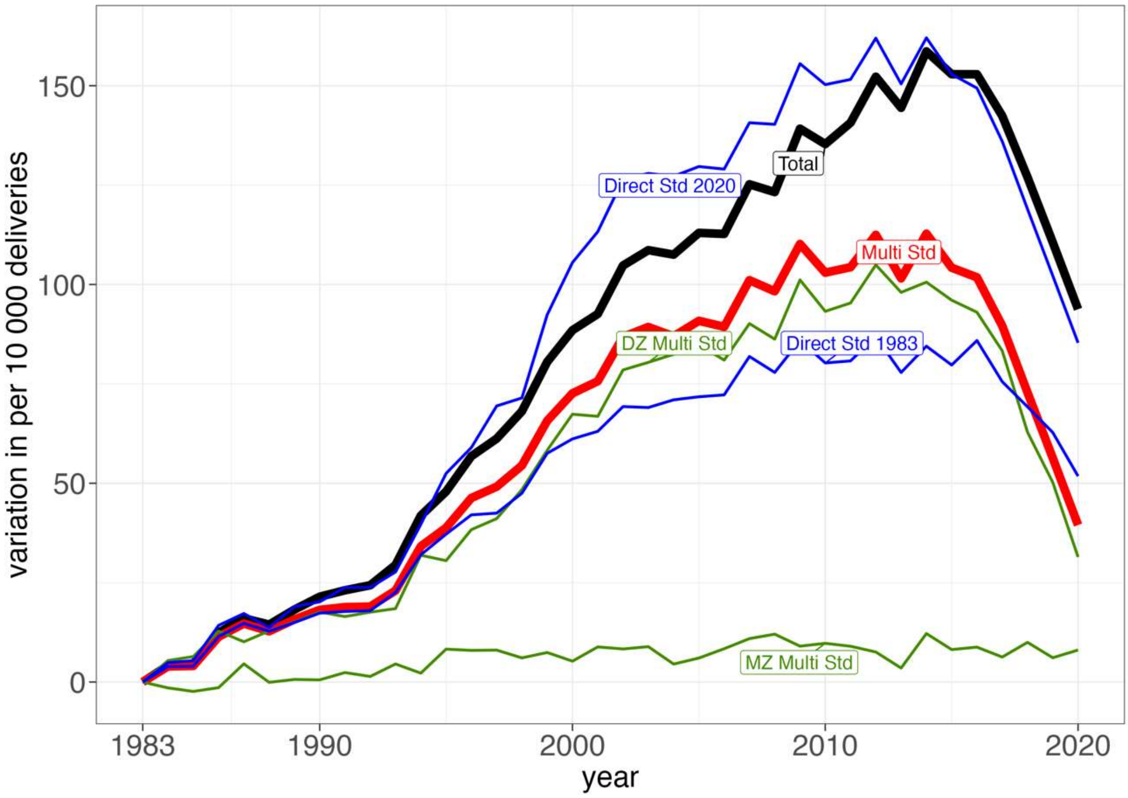
Figure 4-4 Figure 4-4, with a likelihood 3 to 4 times higher between 30 and 40 years of age, and up to 20 times at 45 years of age. However, the probability of having DZ twins has decreased in the more recent period, especially after the age of 40, which explains the decline in total multiplicity. It is also important to observe that the age pattern of DZ multiplicity changed dramatically as a consequence of MAR use, amplifying the effects of the postponement of childbearing ages on total multiplicity.

4.3.2 Increase of multiplicity due to MAR

Figure 4-5 presents different ways of measuring the effect of MAR on the evolution of total multiplicity, as represented here by the absolute change accumulated since 1983 (the "Total" series). Thus, in 2020 its absolute level was 164 and, therefore, the change from its 1983 level of 71 corresponds to an increase of 94 (all values per 10,000 deliveries). Also shown in this figure are five indicators that attempt to directly measure the effect of the use of MAR on multiplicity:

- First is the "Multi Std" series, which is the measure we propose, obtained from formula [4.6].
- The "Direct Std 1983" series corresponds to the results of the classic direct standardisation calculation, taking as standard the proportions of deliveries by age for year 1983. The value represented in this graph corresponds, for each year, to the absolute variation with respect to the 1983 level.
- The "Direct Std 2020" series is computed in the same way than the previous one, but using as standard the age distribution of deliveries in year 2020.
- The "DZ Multi Std" and "MZ Multi Std" series are obtained by using the same methodology as for the "Multi Std" series, but applied to DZ and MZ multiple births respectively (and indeed the "Multi Std" series is the sum of the "DZ multi Std" and "MZ multi Std" series).

Figure 4-5. Effects of MAR on the variation of total multiplicity, according to various estimation methods, years 1983-2020 (absolute variations in per ten thousand of total deliveries)



Source: authors, based on INE Microdata.

Note: ***Total*** is the absolute difference between the current level of total multiplicity of births and its initial level in 1983; ***Direct std 2020*** is again the difference from the level in 1983 of multiplicity measured with a direct standardisation, taking the age distribution of deliveries of year 2020 as a basis, and ***Direct std 1983*** is the difference from the level in 1983 of the values based on a direct standardisation using the distribution of 1983 as standard. ***Multi Std*** is the accumulation of annual terms of multiplicity due to MAR according to formula [4.6] corresponding to our extension of Kitagawa's method of multiple standardisation. ***DZ Multi Std*** corresponds to the same calculation, but applied only to dizygotic multiple births, and ***MZ Multi Std*** is again the same calculation but for monozygotic deliveries.

The first observation is that the use of the classical direct standardisation method can lead to very contradictory conclusions indeed, since the results obtained from the 1983 or 2020 standard are completely different, the former underestimating and the latter overestimating the total observed variation. Unfortunately, as the choice of a year as a standard is arbitrary, it is not possible to decide which of these two series is more correct. Second, we observe that the "Multi Std" series that we propose for measuring the effect of MAR is approximately in the middle of the two previous ones and therefore seems to give a more robust result. Finally, we observe that the effect of MAR on multiplicity is mainly due to DZ twins, although there is also a non-negligible effect of MZ twins, which explains an overall increase of about 10 per 10,000 of total multiplicity.

Table 4-1 presents the absolute and relative contribution of the previous series to the variation in total multiplicity, compared to the results obtained with the classical decomposition methods of Kitagawa (1955) and Horiuchi et al. (2008). Again, it can be seen that direct standardisation, depending on the year chosen for the age composition standard, gives extremely variable and therefore unreliable results, as using year 2020 as standard leads to an estimate of the MAR effect that is double the size of the effect measured when year 1983 is used for the standard. It is more interesting to compare the results of the traditional decomposition methods of Kitagawa and Horiuchi et al. with those of our extension of the multiple standardisation method. The main difference is that, in the latter, all the available information is taken into account, and not only the initial and final year of each period analysed. For example, for the period 1983-2014, the classical decomposition methods attribute 74% of the increase in total multiplicity to the MAR effect, while our method attributes 78% to this, even though these classical methods "explain" an absolute increase in total multiplicity of 117 per 10,000 deliveries out of a total of 159, while our method only explains an increase of 113. This inversion for the relative and absolute effects is only an apparent inconsistency, as our method considers all the intermediate yearly variations and therefore gives a more robust result. The inversion is even more visible for the whole period, from 1983 to 2020, when our method indicates that MAR explains 81% of the variation in total multiplicity, for an absolute increase of 40 per 10,000, whereas the classical decomposition methods lead to an estimate of the MAR effect of only 73%, for an absolute increase of 69. The 2014-2020 period of decreasing total multiplicity shows another feature of our measure of the size of the relative effect as, in that period, the decrease of -72 in the MAR effect as measured by the traditional decomposition methods was larger in absolute terms to the decrease of -65 in total multiplicity. The usual interpretation is that MAR "explains" 111% of the total variation (when dividing -71 by -65) and, therefore, the age composition effect contributes -11%, as it varies in the opposite direction, slowing down the decrease in total multiplicity. Our method, which is similar to a variance decomposition, attributes 88% to the MAR effect and 12% to the composition effect in explaining the variation in total multiplicity, which gives a direct reading of the relative importance of both factors (albeit losing the inversion in sign).

Table 4-1. Absolute and relative effect of MAR on variation of total multiplicity calculated by extended multiple standardisation or by direct standardisation, using years 1983 or 2020 as standard, as well as by Kitagawa and Horiuchi et al. methods (values in per 10 000 deliveries and in % of total variation).

		1983-2014	2014-2020	1983-2020
Variation in total multiplicity	ΔM_t	159 (100%)	-65 (100%)	94 (100%)
Variation in Direct Standardisation Index	$\Delta M_t^{Dir_{1983}}$	85 (53%)	-33 (50%)	52 (55%)
	$\Delta M_t^{Dir_{2020}}$	162 (102%)	-77 (118%)	85 (91%)
Extended Multiple Standardisation Index	${}_tM_0^{MS}$	113 (78%)	-73 (88%)	40 (81%)
Kitagawa (1955) and Horiuchi et al. (2008)		117 (74%)	-72 (111%)	69 (73%)

Source: Authors based on INE Microdata.

Note: ΔM_t is the absolute variation during each time period of total multiplicity. $\Delta M_t^{Dir_{1983}}$ and $\Delta M_t^{Dir_{2020}}$ are the absolute variation of the direct standardisation indexes based respectively on the distribution of deliveries by age of years 1983 and 2020. ${}_tM_0^{MS}$ is the value of the aggregated multiple standardisation index as per formula [4.6]. Kitagawa (1955) and Horiuchi et al. (2008) represent the MAR effect corresponding to the application of each of these two decomposition methods. Values in parenthesis correspond to the relative effect of MAR on the variation of total multiplicity. For direct standardisation, and for Kitagawa and Horiuchi et al. methods, this relative effect is computed directly: for example, for $\Delta M_t^{Dir_{1983}}$ during the 1983-2014 time period, the variation of 85 represents 53% of the total variation of 159. On the contrary, for ${}_tM_0^{MS}$ the relative effect corresponds to the "variation potential" of formula [4.5].

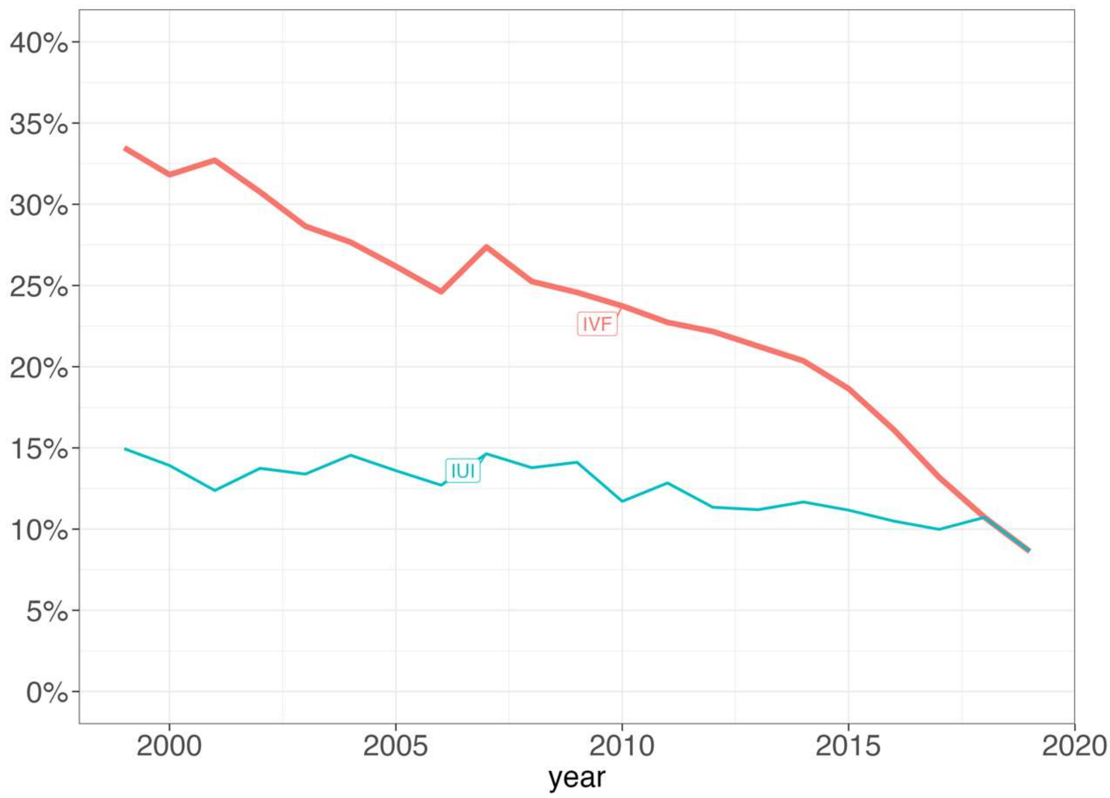
4.4 Estimating the number of births initiated by MAR treatments in Spain from multiplicity data

The aim of this section is to build on the previous estimates of the number of multiple deliveries due to MAR treatments to assist us in analysing data from the Spanish IVF and IUI registers and, finally, to obtain an estimate of the proportion of births initiated by these treatments in Spain.

4.4.1 Multiplicity of deliveries due to MAR treatments in the SEF registry

Figure 4-6 presents the multiplicity of deliveries due to MAR treatments carried out in Spain, with figures obtained from the SEF annual reports, assuming that these data are representative of all the clinics, even in the period when less than half of them participated in the register. Multiplicity of deliveries resulting from IVFs fell sharply in this period, due to the causes indicated above. This drop is especially significant from 2014 onwards, with a reduction to half of this proportion, which explains the accelerated decrease in total multiplicity observed in figure 4-1. In comparison, the reduction in multiplicity of deliveries started with an IUI appears to be smaller but, nonetheless, with a decline of one third in the period.

Figure 4-6. Multiplicity of deliveries started with IVFs and IUIs in years 1999-2019 according to SEF registries



Source: authors based on reports of *Sociedad Española de Fertilidad* (SEF) registries.

Note: we assume here that multiplicity reported by clinics before year 2014 is representative of the whole set of centres.

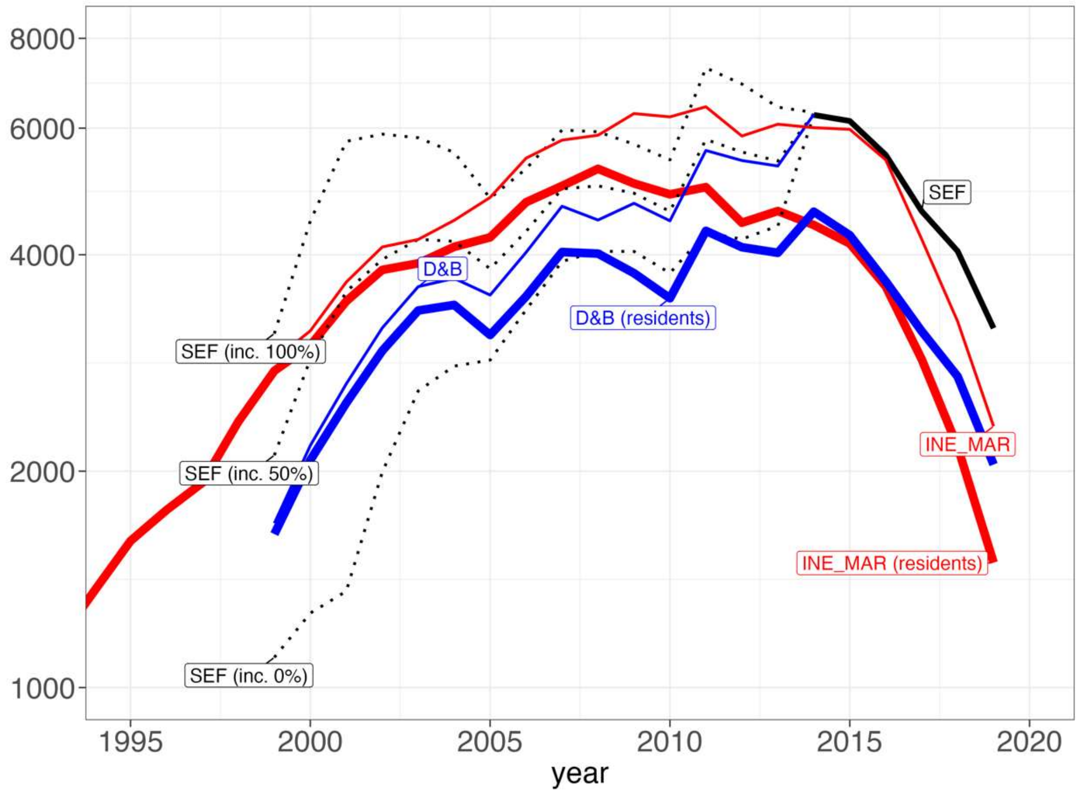
4.4.2 Comparing SEF and INE data

Figure 4-7 allows us to judge the reliability of the SEF registers and the series that can be derived from it, from an estimate of multiple deliveries due to MAR obtained with our method, using deliveries data from the Spanish Statistical Institute (INE). As mentioned above, the SEF registers are exhaustive only from 2014 onwards. We observe that, starting from this year, the data estimated by our method (*INE_MAR (residents)*: which was "*Multi Std*" in Figure 4-5) are between 30% and 50% below the *SEF* series. This is probably due to the treatments of women residing abroad. These are included in the SEF series presented, which collect information from pregnancies due to IVFs and IUIs carried-out in Spanish clinics, but do not figure in the INE data, which inform only on deliveries by women resident in Spain. This is confirmed by the *D&B (residents)* series, which is based on SEF data, but with a correction for excluding the deliveries from non-residents, estimated to represent between 30 and 35% of total IVF treatments in the years 2015-19.

Demand from abroad is such an important factor that we have constructed an alternative series based on INE data that incorporate multiple deliveries which occurred outside Spain. This is obtained by increasing the figures from the multiple standardisation method using the correction factors for this foreign demand estimated by D&B from SEF data. This new augmented series is called *INE_MAR* in figure 4-7. Hence, the data in this new series coincide almost perfectly with those of the SEF for the period 2014-16, which testifies to the precision of our method. However, there is a systematic downward deviation starting from 2017. This may be due to a limitation of the multiple standardisation method, but another, more substantive, explanation is that the IVF treatments of a part of the women residing abroad follow a different protocol, which could lead to higher multiplicity. Indeed, the notable decrease in multiple deliveries from 2014 onwards can be explained mainly by the generalisation of single embryo transfers, with the first cycle involving the collection of several fresh eggs that are fertilised, most of which are cryopreserved for later transfer, in case of failure. This new strategy assumes that the patient is treated over a period of several months, which is easier for women who reside in Spain. It can therefore be assumed that some women living abroad prefer transfers of several embryos, in order to increase the probability of success of each cycle and minimise trips to the clinic. If this totally hypothetical explanation is correct, it would explain why a greater drop in multiplicity is observed in the INE data, which refer to residents in Spain, than in the SEF data, of which approximately one third correspond to non-residents.

For the period before 2014, when the SEF registries were not exhaustive, there is greater uncertainty. In order to compare the SEF data to the series of multiple deliveries due to MAR that we derive from INE data, we have built three alternate series based on different assumptions about the size of the clinics that did not participate in the registries: same mean number of treatments as that for those which participated - *SEF (inc. 100%)*, or half that number – *SEF (inc. 50%)* – or no treatment at all – *SEF (inc. 0%)*. Based on the *INE_MAR* series, the relative size of clinics that did not report to the SEF was probably somewhere between 50% and 100% of those that did in the period 2000-2013, when the estimates made by D&B from SEF data are based on assumptions that this relative size was lower than 50%. In this sense, the latter series possibly underestimates by 10-30% the numbers of multiple deliveries due to MAR treatments that we derive from INE data. Obviously, these conclusions critically depend on the accuracy of the estimates made with our multiple standardisation method, which allows the INE_MAR series to be obtained. These estimates are based on the sum of variations in multiplicity with levels hovering at around 1 to 2% of the deliveries. Hence the results may incorporate a stochastic process similar to a random walk and it is probably better to consider the INE_MAR series as correct in its trend of evolution, and not to focus on its short-term variations.

Figure 4-7. Number of multiple deliveries due to MAR. Comparison between estimates based on INE and SEF data



Source: D&B for the two series in blue, and our own estimates based on reports of SEF registries and INE data for the rest.

Note: Logarithmic scale for the number of deliveries.

- ***INE_MAR (residents)*** is our estimate of the number of multiple deliveries corresponding to the series ${}_tM_0^{MS}$ applied to INE data (it was named "*Multi Std*" in figure 4-5);
- ***INE_MAR*** is the same series augmented to incorporate deliveries by women who reside abroad (using the inflation factor obtained dividing the *D&B* by the *D&B (residents)* series);
- ***SEF*** is the number of multiple deliveries started from IVFs or IUIs as reported by the SEF registries in the 2014-2019 period, when these registries were exhaustive;
- ***SEF (inc. 0%)*** is the (incomplete) series of multiple deliveries starting from IVFs or IUIs as reported by the SEF registries in the 1999-2013 period, when not all the clinics reported (and taking that series at face value would implicitly suppose that the clinics that did not report had no activity);
- ***SEF (inc. 50%)*** and ***SEF (inc. 100%)*** are the estimated series for the period 1999-2013 supposing that the clinics which did not inform the SEF carried out, respectively, half or the same mean number of treatments as the clinics that reported them;
- ***D&B*** are the multiple deliveries counts derived from the estimates made by Devolder and Borisova (2022), based on SEF data;

- ***D&B (residents)*** is the previous series but restricted to women who reside in Spain. The number of multiple deliveries started from IUIs and obtained from SEF data are inflated by a factor of 10% to account for deliveries resulting from Programmed Intercourses.

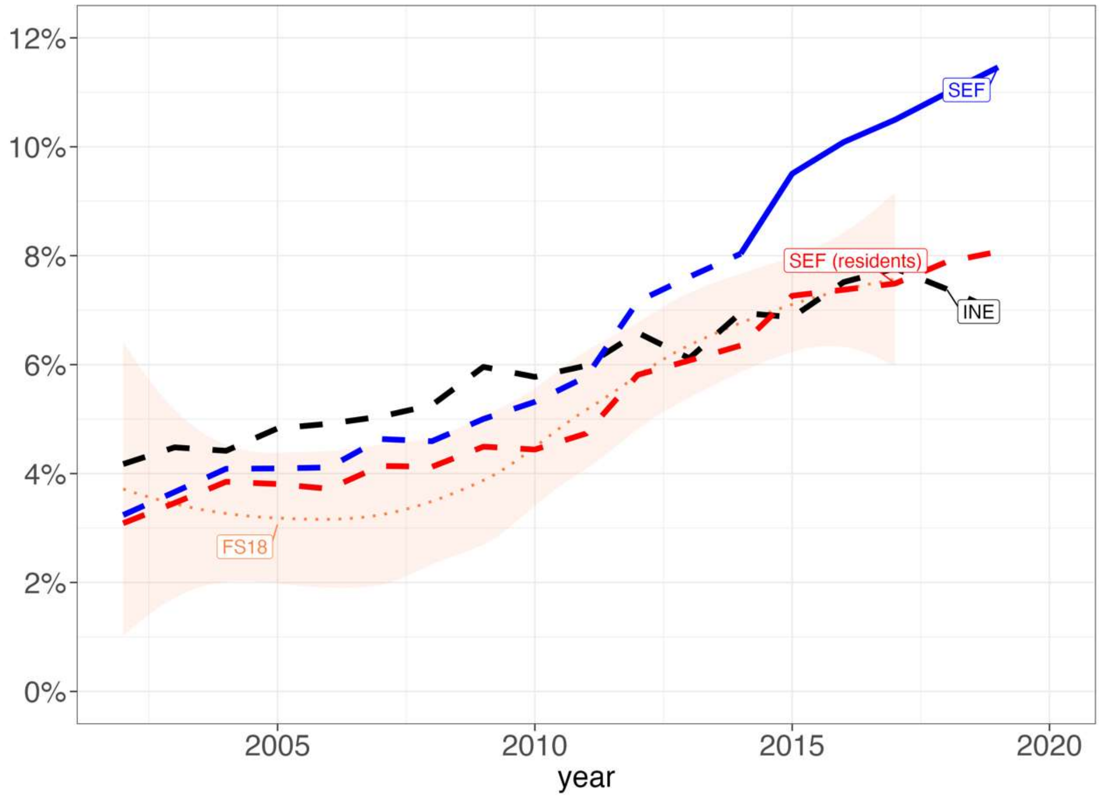
4.4.3 The weight of births due to MAR treatments

Finally, we change the scope of our study by focusing on the contribution of MAR treatments to Spanish births, which also allows us to refine the previous analysis on the quality of the estimates obtained from the SEF data and by the multiple standardisation method. For this purpose, we constructed a series of births due to MAR obtained from the series of multiple births estimated by our method from INE data. This series is compared to two series derived by D&B from the SEF registries, one for all women treated in a clinic in Spain, and the other one only for residents, as well as to a series obtained from the 2018 Spanish fertility survey. This survey allows us to know whether a woman has undergone assisted reproductive treatments and which one, since what age, and whether this has allowed her to have one or more children, which enables us to construct an alternative series of the proportion of births due to MAR. These four series are presented in figure 4-8.

Again, we can start the analysis from year 2014 onwards, when the data from the SEF registries are complete. We observe, then, an almost perfect coincidence between the fertility survey series, the one derived by D&B for resident women from the SEF registries, and the series obtained from our multiple standardisation method. However, the proportion corresponding to total births registered by the SEF is at a much higher level, which confirms that the demand for patients residing abroad is probably much higher in the recent period than the figure of 10% indicated by the official registers. It is interesting to note that according to these estimates, 8% of the births in Spain in 2019 are obtained by a MAR treatment, a level comparable in Europe only to Denmark. However, if we do not exclude the demand from non-residents, we would arrive at a proportion of 11.5% in 2019.

On the other hand, for the period before 2014, the 2018 Spanish fertility survey data are closer to the series derived by D&B from the SEF data than to the one obtained by our method, which consequently seems to overestimate the number of births due to MAR before 2010.

Figure 4-8. Proportion of births in Spain due to MAR treatments. Comparison of estimates from SEF registries, the 2018 Spanish Fertility Survey and INE data



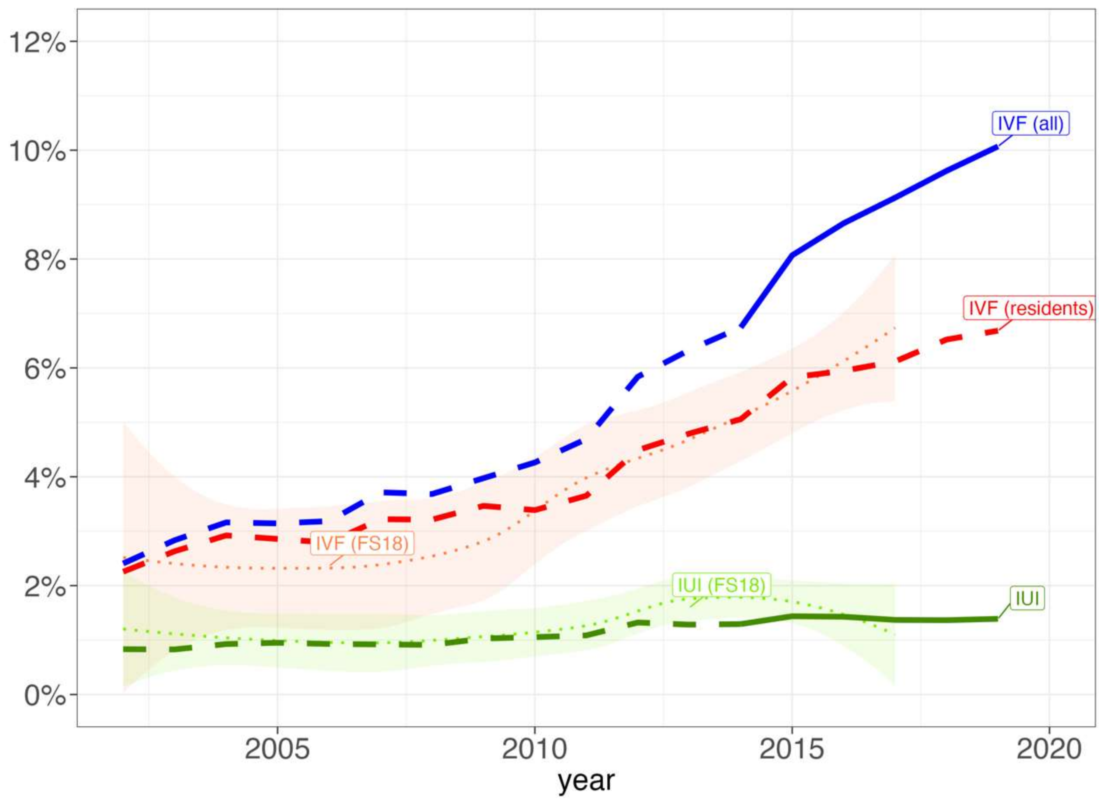
Source: D&B for the SEF series and authors' estimates based on INE data and 2018 Spanish Fertility Survey.

Note: ***SEF***: proportion of births started from IVFs and IUIs, as reported by the SEF registries, with the corrections from completeness before 2014 and deliveries lost to follow-up implemented in *D&B* (note also that births from IUIs are inflated 10% to take account of PIs); ***SEF (residents)***: same series, but counting only the births of women who reside in Spain, as explained in *D&B*; ***FS18***: proportion of births started from a MAR treatment as reported by women in the 2018 Spanish Fertility Survey; ***INE***: number of births from MAR treatments derived from the *INE_MAR* series of Figure 4-7, using the multiplicity proportions of Figure 4-6 weighted by D&B estimates of births started by IVFs and IUIs. The series obtained from the Fertility Survey is smoothed with the Loess algorithm and accompanied by a 95% confidence interval for the fitted curve. The two series based on SEF data are shifted forward 0.75 years in time as births from cycles initiated in one calendar year occur on average 9 months later. The curves with dashed lines are estimates when the SEF registries were not exhaustive.

Figure 4-9 allows breakdown of the previous data by kind of treatments, comparing estimates of the proportions of births started from IVFs or from IUIs (including PIs) obtained by D&B from the SEF registries, and the same proportions derived from the Spanish Fertility Survey. Again, there is a good coincidence between the two types of series. It can be seen that the increase in births due to MAR treatments is mainly due to

IVF, since the weight of births due to IUI and PI increased by only 0.3 points in the last two decades, compared to more than 4 points for IVF.

Figure 4-9. Proportion of births in Spain due to IVFs and IUIs. Comparison of data derived from SEF registries with estimates based on the 2018 Spanish Fertility Survey



Source: D&B and authors' estimates using 2018 Spanish Fertility Survey data.

Note: ***IVF (all)***: proportion of births started from IVFs, as reported by the SEF registry, with the corrections from completeness before 2014 and deliveries lost to follow-up implemented in *D&B*; ***IVF (residents)***: same as *IVF (all)* but counting only the births of women who reside in Spain, as explained in *D&B*; ***IUI****:* proportion of births started from IUIs, as reported by the SEF registry, with the corrections from completeness before 2014 and deliveries lost to follow-up similar to the one applied by D&B to IVFs, and inflated by 10% to include births from PIs; ***IVF (FS18)***: proportion of births started from IVFs as reported by women in the 2018 Spanish Fertility Survey; ***IUI (FS18)***: proportion of births started from IUIs and PIs as reported by women in the same Survey. The two series obtained from the Fertility Survey are smoothed with the Loess algorithm and accompanied by a 95% confidence interval for the fitted curves. The three series based on SEF data are shifted forward 0.75 years in time as births from cycles initiated in one calendar year occur on average 9 months later.

4.5 Discussion

The main contribution of this study is an improvement in standardisation methods for the study of variations over time of a rate or proportion. The results obtained by the classical direct or indirect standardisation methods are far too sensitive to the choice of a year as standard. Our extension of Kitagawa's multiple standardisation method obtained by merging it with the more general decomposition approach of Horiuchi et al. allows for a better estimation of the effect of MAR on multiplicity. However, multiple standardisation is an appropriate method only for the study of variations of a rate over time and, therefore, it cannot in principle be a general substitute for simple standardisation, since the core of the method is pairwise matching of successive terms of the series, which will not serve, for example, in the case of a comparison between more than two populations. Note that, here, we apply it to the case of the variations of a proportion according to a single characteristic, age, but it can be extended to the case of several others, either by using the approximate method of Horiuchi et al. (2008), or the exact method of Das Gupta (1991).

A second result of this study is an estimation of the total number of births obtained by MAR treatments from the study of its effects on multiplicity. However, as the proportion of multiple births is low, between 1 and 2% of deliveries, this may have the disadvantage of short-term instability of the results, as our method uses the accumulation of differences that therefore incorporates a non-negligible stochastic component, which may lead to deviations from the trend value. It should also be pointed out that, in the attempt to ascertain the effect of MAR on the birth rate, the fact that a large part of the patients treated are in fact subfertile must be taken into account and, moreover, some would have achieved a birth by natural means, as shown by Léridon (2005) using a fertility microsimulation model. Hence, MAR treatments often only hasten births, albeit with substantial economic and psychological costs.

Another finding is establishing that the increase in total multiplicity is mainly due to DZ twins, although the share of MZ twins is higher than one would expect, which corroborates the clinical observations reported above.

Finally, we confirm D&B's result regarding the proportion of IVF carried out in Spain for women residing abroad, which reaches a high level of around 35% in recent years, when the official figure is about 10%. As a consequence, it is possible to obtain a proportion of births due to MAR treatments of only 8% in Spain in 2020, which puts this country in the lead at the European level, rather than the 10.5% that would be obtained with the uncorrected data from the registry of these treatments. More generally, studying the effect of MAR on births is complicated by a lack of detailed data on the origin of the women in the countries that receive them, which does not allow determination of the full effect on births and fertility in the countries of origin. By way of example, births from IVFs of non-resident women that occurred in 2017 in Belgium, Czechia, Denmark, Greece, and Spain, the main countries of destination in Europe for "reproductive tourism", represented approximately 20% of the total of IVF births occurring this year in Germany, France and Italy, the main countries of origin (estimate based on ESHRE data published by Wyns et al., 2021).

CAPÍTULO V.- Measuring IVF success for each embryo transferred and detecting the effect of embryo synergy at an aggregate level[9]

"El éxito llega para todos aquellos que están ocupados buscándolo".

Henry Thoreau

Resume

Traditional indicators of the success of in vitro fertilization (IVF) computed with aggregate data do not properly take into account the number of embryos transferred, which is a huge limitation in the context of the growing importance of Single Embryo Transfers and, more generally, of large variations in the last decades in the distribution of cycles or transfers in terms of the number of embryos transferred.

We devised an indirect method for computing the probability of a live birth per embryo transferred starting from the Live Birth Rate (LBR) calculated for transfers with a specific number of embryos. This allows comparison of transfer success over time or between countries, as well as between eggs of different origin or process (own- or donated- as well as fresh or frozen), controlling for the number of embryos transferred. We also computed this probability with a direct method similar to the Implantation Rate, which can be used for a few countries with detailed registries.

We used both methods using aggregated registry data for seven countries, as well as Latin America. The difference in the level of this probability obtained with both methods allowed us to detect the effect of embryo synergy, when the implantation and survival of one embryo increase likelihoods of both prospects for other embryos transferred at the same time. This synergy effect could account for around a 15% increase in the number of live births for transfers of two embryos.

We propose a new way of measuring IVF success at an aggregated level, which could complement the LBR and other similar indicators in a new and important way.

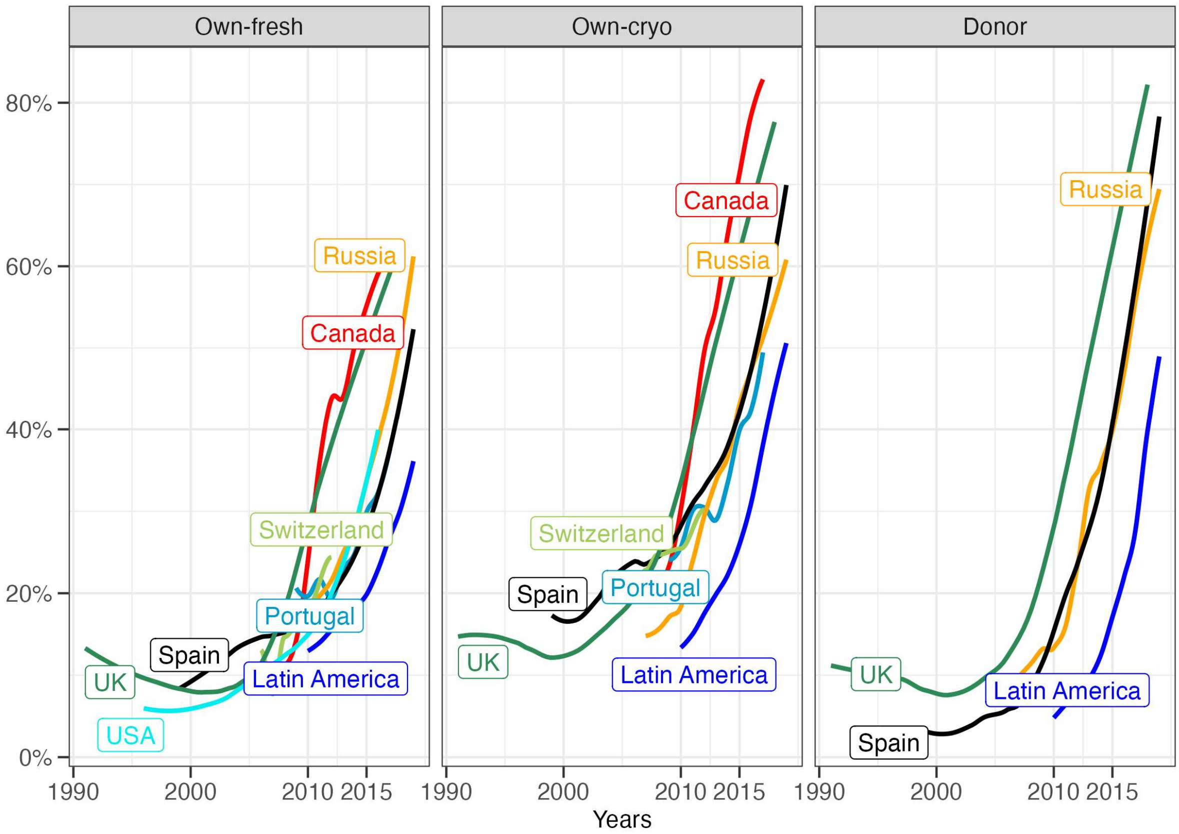
We detected and measured the embryo synergy or collaboration effect with aggregated registry data which, as far as we know, has never been done before.

[9] This chapter is realized in collaboration with Daniel Devolder

5.1 Introduction

There has been considerable change over the last decade in the strategy recommended by medical societies for the use of In Vitro Fertilization (IVF), to favour Single Embryo Transfers (SETs). This new strategy complicates analysis of IVF success, as published data from national registries are usually for individual cycles, which prevents calculation of cumulative indicators, from cycle to cycle, that cover the whole treatment, such as those published at the national level for the USA or the UK (Wilkinson, Roberts, and Vail 2017). It also makes it difficult to compare success for individual cycles over time, due to the very rapid reduction, in the recent period, of the number of embryos per transfer. This can be observed in figure 5-1, which presents the proportion of SETs for a selection of countries, and shows that there has been a transition since 2010 from less than 20% to more than 50% for the transfers of fresh own eggs, and from less than 30% to more than 70% for frozen own eggs. In this paper we introduce a new way of measuring IVF success with aggregate data, controlling for the number of embryos transferred, which could help in comparisons in time and across countries. The formula for this new indicator is based on an extension of the binomial model. The results differ from the ones obtained with an indicator equivalent to the Implantation Rate, which we interpret as the result of a synergy or collaboration effect, where the implantation of a first embryo increases the likelihood of implantation and survival during pregnancy of others transferred at the same time.

Figure 5-1. Proportion of SETs in the total of embryo transfers, according to the type of egg and process, Canada, Latin America, Portugal, Russia, Spain, Switzerland, UK, USA period 1990-2019



Source: National ART registries data and REDLARA for Latin America. Data smoothed with the Loess algorithm using a span factor of 0.5.

5.2 Material and methods

We use national ART registries for which data distributed by number of embryos transferred is provided. We employ a modified binomial model and use a metric comparable to Implantation Rate to determine the probability of a live birth per embryo transferred at an aggregated level.

5.3 Results

5.3.1 Measuring the success of IVF

The study of IVF success is a complex matter, due to the multiplicity of events in the chain from ovarian hormone stimulation prior to egg retrieval through to delivery and birth. Hence, clinical studies at the individual level manage numerous indicators, based on dozens of possible numerators and denominators (Wilkinson et al. 2016). But at an aggregate level, with data from a national registry, success indicators are generally calculated by considering either the number of patients, of cycles initiated, or of embryo transfers as the denominator, and pregnancies, deliveries or live births as the numerators. The points of view of patients and doctors do not coincide and the former probably prefer to know the probability of having a healthy child, even if they have to go through several cycles and embryo transfers, while medical doctors are more attentive to the probability of implantation of each embryo transferred (Fauser 2019). In this sense, current recommendations from fertility societies (Cutting 2018) are to favour the transfer of a single embryo, to reduce the risk of multiple births, followed, if necessary, by further transfers of a cryopreserved embryo obtained in the initial cycle. These recommendations are criticised by analysts who note that they appear to have led to a decline of IVF success per cycle (Gleicher, Kushnir, and Barad 2019) and to especially low levels in Japan of the probability of having a live birth (Kushnir et al. 2017).

The Live Birth Rate (LBR) is the most widely used measure of success in IVF. This is obtained by dividing the number of deliveries with at least one live birth either by the number of cycles or the number of transfers (Zegers-Hochschild et al. 2017). The number of cycles seems, at first, to be the most appropriate numerator, as it is more informative for patients. However, the proportion of freeze-all cycles (when all the retrieved eggs are frozen) has increased sharply in the recent period, and some national registries do not exclude them from the total of cycles when, on the other hand, the proportion of cancelled cycles has also increased significantly in numerous countries, and both evolutions may confuse the analyst. Thus, in the USA, the proportion of cycles, excluding freeze-all cycles, cancelled before the embryo transfer increased markedly, from 19% in 2012 to 39% in 2016, which led to a drop in the LBR per cycle in that period, and which (Gleicher et al. 2019) explained by the rise of SET when, in fact, LBR per transfer increased slightly as we show below. The difference between the number of cycles and of subsequent transfers is also highly variable depending on the type of eggs so, for example, the difference for cycles with fresh own eggs is much higher than that for cycles with frozen eggs or embryos, or donor eggs. It is therefore much easier to compare the effectiveness of IVF with eggs of different origins, taking the embryo transfer as the starting point, and thus to favour the LBR per transfer over per cycle. However, the main shortcoming of both indicators is that they do not take into account the number of embryos transferred, which makes it difficult to interpret their variation over time, and whether they are due to an improvement in the overall effectiveness of IVF, or to a composition effect because of variation in the average number of embryos transferred. Partly in order to address this issue, (Abdalla, Bhattacharya, and Khalaf 2010) introduced the Live Birth Rate per Embryo (LB_emb) which is a modification of the LBR per transfer where the denominator is the total of embryos transferred instead of the number of transfers. This penalises transfers of more than one embryo, as LB_emb rate decreases when the number of embryos transferred increases. Both LBR and LB_emb can be used to measure patient-centred outcomes, computing cumulative rates over various cycles, which are now routinely reported in the USA and the UK in national registries reports (Wilkinson et al. 2017).

We propose here to complement LBR and LB_emb with an indicator of average success per transferred embryo, which would somehow represent the medical doctor’s point of view.

5.3.2 Probability of a live birth per embryo

This new indicator measures the probability of success for each embryo, according to the number transferred. It is important to point out, first, that this way of proceeding is not usual and, to the best of our knowledge, it is even the first time that this indicator of success per embryo is calculated at an aggregate level. In the clinical field, a similar indicator known as the "Implantation Rate" (IR) is used, and this is obtained by dividing the total number of embryos implanted by the total number transferred, for all the transfers, or separating transfers according to the number of embryos. Using an ART registry with aggregated data, this rate can be calculated from two types of data in the numerator: counts of initiated gestations, from which we will obtain the direct equivalent of IR, or number of live births, and in this case, we will speak of a probability of one live birth for each embryo transferred. But, in general, we cannot directly use the formula for IR which is based on individual data, since in aggregated registries, pregnancies or deliveries are not always cross-classified by multiplicity of pregnancies or deliveries and number of embryos transferred, so the IR or the equivalent probability for deliveries often cannot be calculated directly. We can do it indirectly if we start from the proportion of transfers that result in a pregnancy, or that end in delivery with at least one live birth. Both are binary indicators (success versus failure) that do not consider multiplicity. However, if we can calculate them separately by number of embryos transferred, then we can use the binomial model to obtain a probability for each embryo, using the formula for the probability of obtaining at least one success, which is the inverse of the probability of failure:

$$LBR_n = 1 - (1 - p_n)^n \qquad \textbf{\textit{[5.1]}}$$

Here, we will use as outcome the number of deliveries with at least one birth, which is LBR per transfer mentioned previously, but calculated separately for transfers with the same number n of transferred embryos. The unknown here is p_n, the mean probability of one live birth per embryo, in transfers of n embryos, which is obtained solving this polynomial of degree n, and choosing the only root whose value is real and positive (it is easy to show that there is only one real root, which is always positive, when the degree is odd, and that there are only two real roots, one negative and one positive, with the same absolute value, when the degree is even, the rest of the roots being complex in both cases). This probability can then be computed directly, retaining the positive real root:

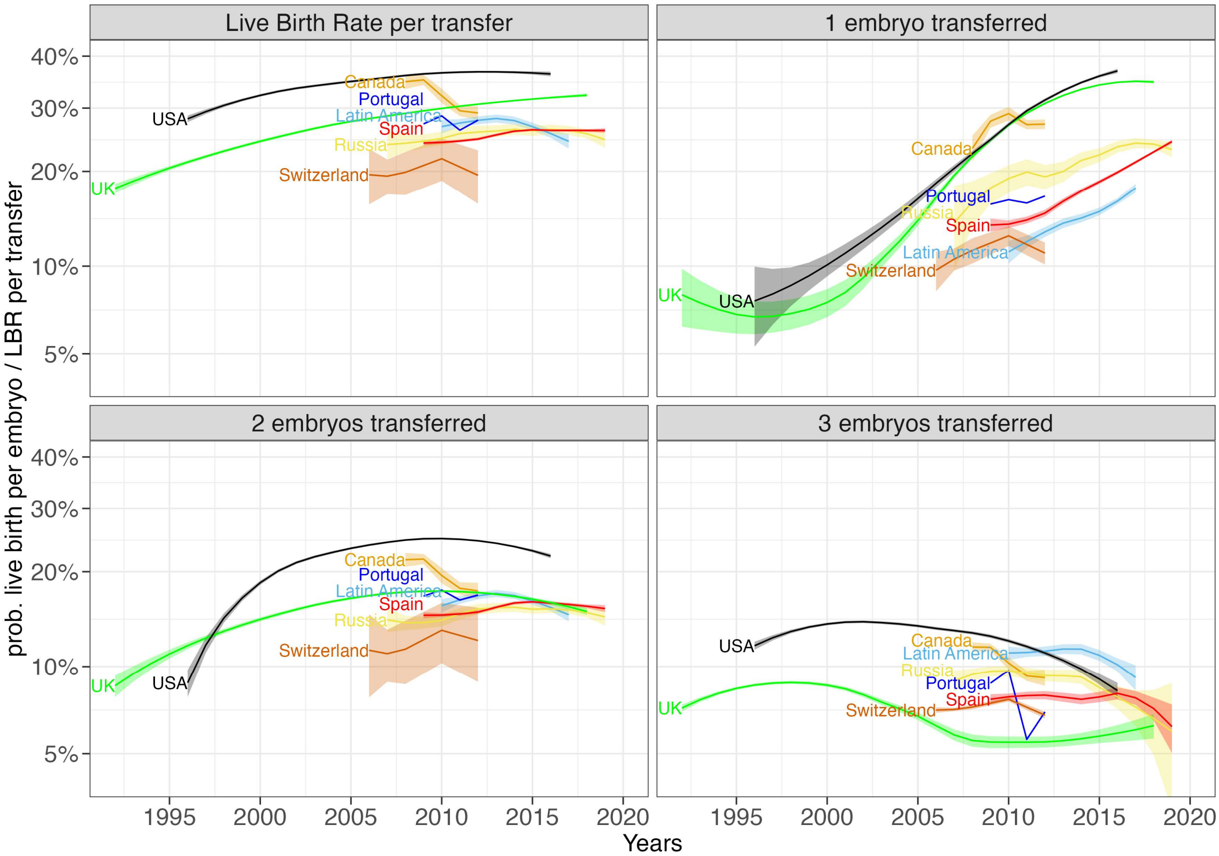
$$p_n = 1 - (1 - LBR_n)^{1/n} \qquad \textbf{\textit{[5.2]}}$$

We therefore assume that the binomial law is a suitable model, considering that the probability p_n is the same for all the embryos in a single transfer, but that its value may change with the number n of embryos transferred. This is both an application and a modification of the usual approach, see for example (Matorras et al. 2005), which starts from the binomial law with a single value of the parameter p, equal for all type of transfers, adding then other parameters to model the effect of the variation of the number of embryos transferred. The models described by these authors are of an explanatory or predictive type when our approach is purely one of measurement, so we do not aim to predict the level of p_n when n changes.

5.3.3 Comparing IVF success per embryo across countries for fresh own eggs

Figure 5-2 presents LBR per transfer, for all transfers, and the probabilities of a live birth per embryo for IVF with fresh own eggs, computed separately for transfers of 1 to 3 embryos, for 7 countries plus a group of countries in Latin America, in the last two decades. We observe that the level of LBR was highly variable across countries, when its evolution over time was quite similar, with a slowdown in growth, and even a decline for some countries at the end of the period. On the other hand, the evolution over time of the probabilities per embryo was quite different, with a rapid and steady increase for transfers of one embryo when, for transfers of two or three embryos, there was stagnation before 2010, and a slight regression afterwards. This new indicator reveals that the level of probability per embryo for transfers of one was lower than for transfers of two, and even for transfers of three before 2005, when its strong upward surge later led it more recently, in Spain, Russia, and the UK, to almost double the level of probability per embryo for transfers of two, and triple that for transfers of three embryos. Generally speaking, an important observation is that the use of the probability per embryo makes it possible to reveal that the well-known difference in IVF success between Spain (and the rest of the European countries) and the USA exists mainly for single embryo transfers.

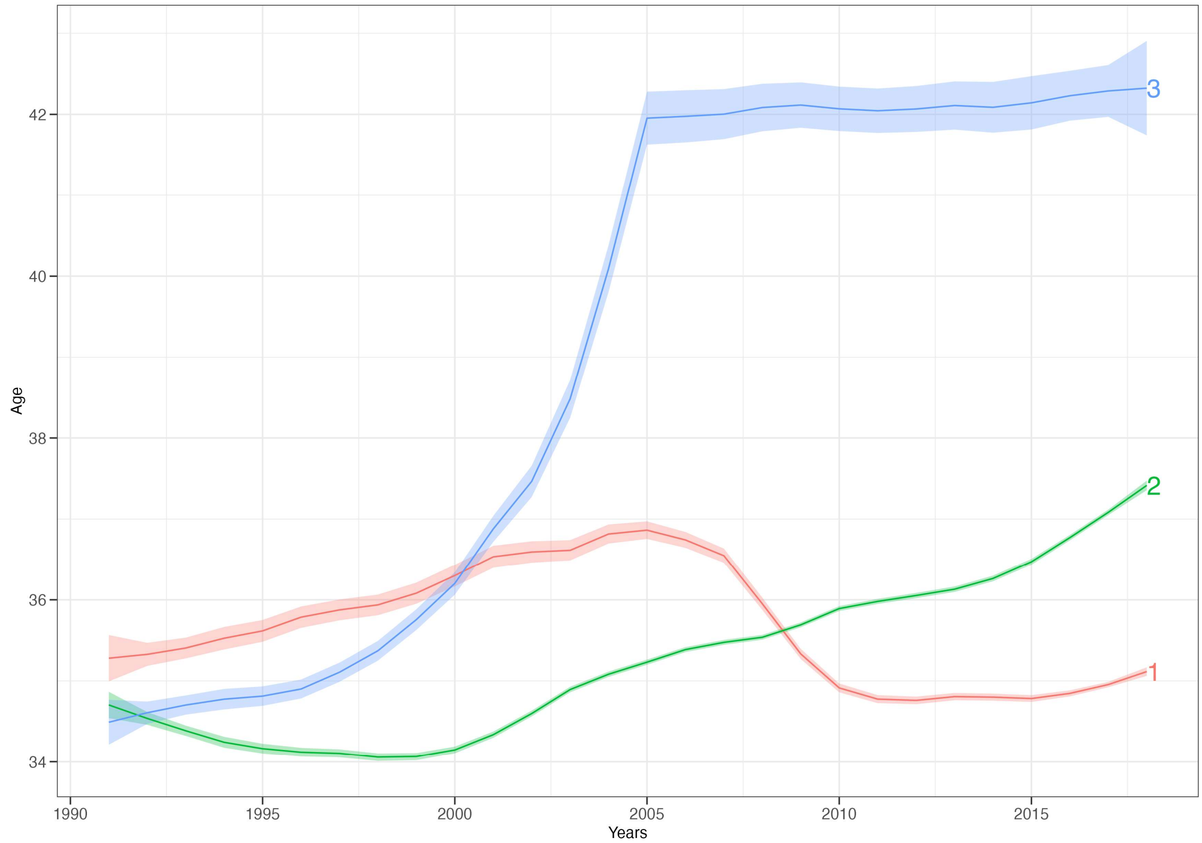
Figure 5-2. Live Birth Rate per transfer for all transfers and probability of a live birth per embryo, according to the number of embryos transferred, for IVF with own fresh eggs.



Source: Canada, Latin America, Portugal, Russia, Spain, Switzerland, UK, USA, period 1992-2019. Data derived from national ART reports of the respective countries, and from the REDLARA international registry for Latin America.

It may be useful to try to explain the observed evolutions. The very rapid increase in the success of single-embryo transfers is probably due in great part to a change in the IVF protocols in these countries. Recommendations of professional societies that favour single-embryo transfers actually make sense for young women, with good quality embryos when, for older women, or in cases of lower quality embryos, it will be more common to continue with transfers of more than one embryo. Embryo quality detection methods are still time consuming, but have improved in recent years (Tiitinen 2019), and they are now used routinely, as studies have shown that the clinical pregnancy and live birth rates per transfer are nearly twice as high with the transfer of a single good quality embryo than with the transfer of a poor quality embryo (Oron et al. 2014). In other words, the increased success for single-embryo transfers could probably be explained by an age effect, namely younger patients, and/or to a higher embryonic quality, which in turn could explain the lower success rate for transfers of two or three embryos: a greater number of older women and/or more cases with lower quality embryos with time. In order to determine the extent to which these factors play a role, and what the residual effect of improved techniques in increasing IVF success, it is necessary to have individual data with sufficient information (at least age and embryo quality) and to use an appropriate statistical model, which is not possible with the aggregated registers from these countries. Data from UK partially demonstrate this hypothesis, as figure 5-3 shows that the mean age of patients for transfers of one embryo with fresh own eggs dropped abruptly after 2005, when the age for transfers of two and especially of three embryos increased sharply.

Figure 5-3. Mean age of patients at treatment by IVF with fresh own eggs according to the number of embryos transferred, UK, 1991-2018



Source: Data derived from UK registry microdata files (HFEA). The series are smoothed with the Loess algorithm, with a span value of 0.28 (Cleveland & Grosse, 1991) using the numbers of patients as weights, which allows computing a 95% confidence interval for the curves (the region where 95% of the fitted curves obtained with similar sets of data would be found). We use the following mean ages for each age group:

Age group	18-34	35-37	38-39	40-42	43-44	45-50
Mean age	32	36.5	39	41	44	46

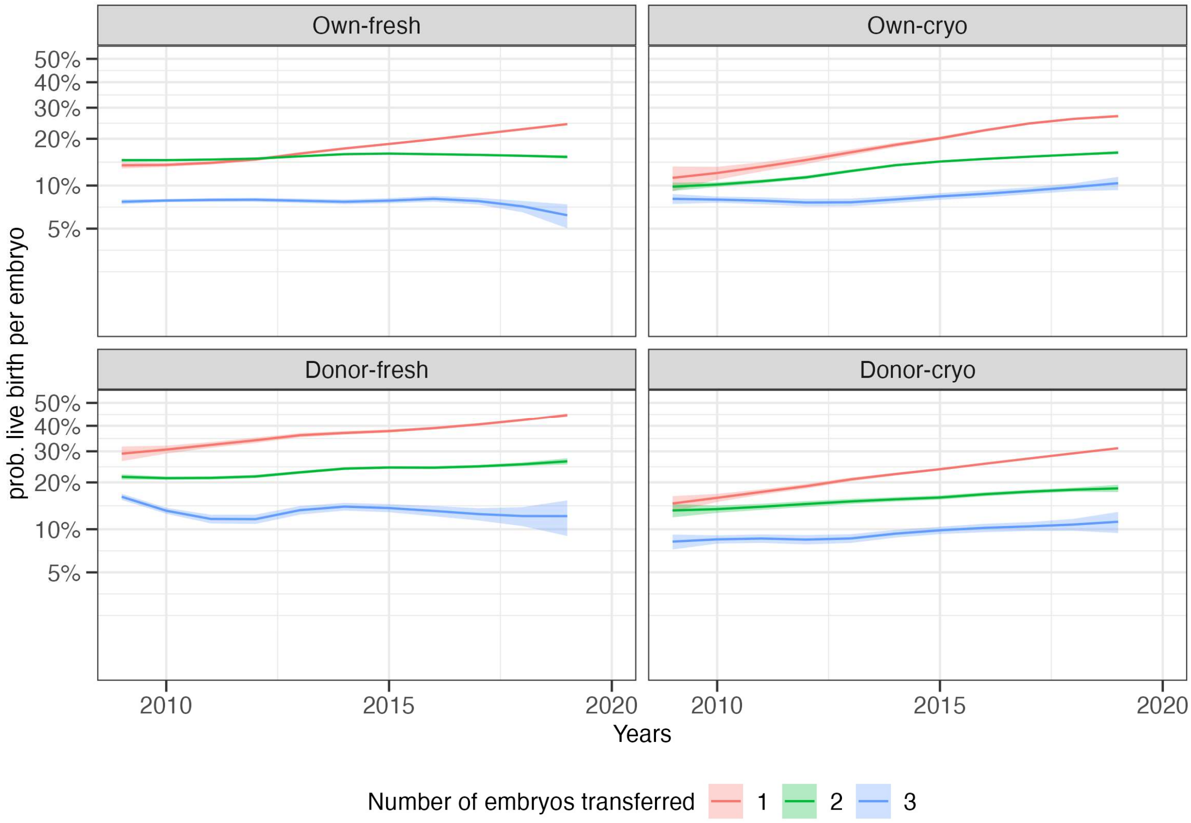
The probability of success per embryo is obtained by applying the binomial law, as explained in the text. The rate and probabilities are represented using a logistic scale. The series are smoothed with the Loess algorithm, with a span value of 0.75 (Cleveland & Grosse, 1991) using the numbers of deliveries as weights, which allows computing a 95% confidence interval for the curves (the region where 95% of the fitted curves obtained with similar sets of data would be found). Deliveries for Portugal, Spain and Russia include a correction for clinical pregnancies lost to follow up.

5.3.4 Success of each embryo according to the origin of eggs

As we said before, this new indicator is especially interesting for comparing success according to the origin of eggs. Figure 5-4 presents this data for Spain (and figures 5-5 to 5-7 for the UK, Russia and Latin America as well). It is important, first, to take into account the observations made for the previous graph: the comparability of levels and evolutions, and even between egg origins, can be conditioned by the effects of age of patients or quality selection of the embryos, and it would be desirable to control for them statistically so that only the variation in probabilities due to improved techniques and/or clinical practices would be analysed.

Nevertheless, it can be seen for Spain that the most significant improvements occurred for single-embryo transfers since, for all four types of eggs, this is the probability that increased the most, as well as being the type of transfer that became predominant (as seen with figure 5-2). But the gap between probabilities remained small for transfers of fresh own eggs when, by contrast, for eggs from donors or cryopreserved, the level of probability for transfers of one embryo in recent years almost doubled the level for transfers of two, meaning that the corresponding LBR of both should be almost equal. This could be a justification for choosing single-embryo transfers, which is not the case for IVF with fresh own eggs, for which the transfer of two embryos still seems to be the most probable way of obtaining a live birth. The UK stands out as the country with the highest level of the probability of a live birth for SET with fresh own eggs, a level that is almost twice that for transfers of two. In the UK also, and with Spain as well, the probabilities for all transfers are especially high for fresh donated eggs. Furthermore, in the last decade, the probabilities for all transfers have progressed the most for cryopreserved own eggs for the three countries and Latin America.

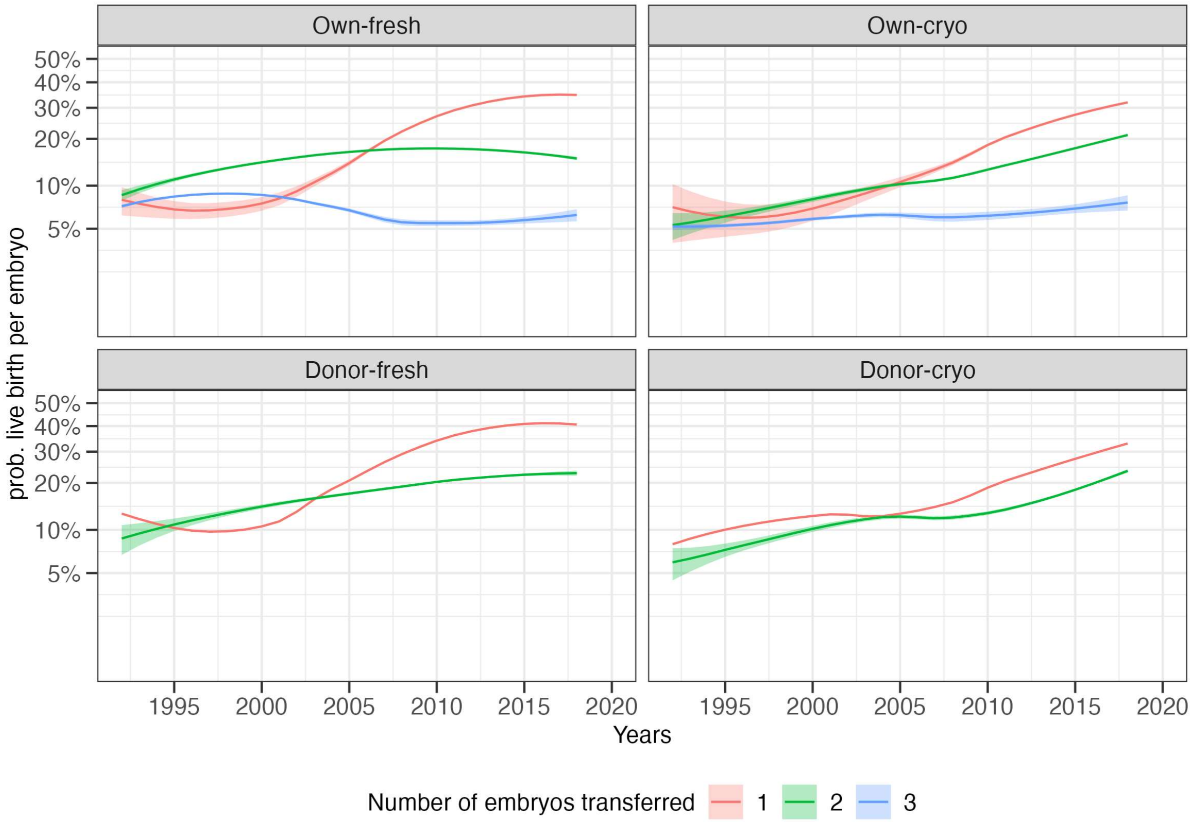
Figure 5-4. Probability of a live birth per embryo, according to the number of embryos transferred and the origin of eggs, Spain for the period 2009-2019



Source: Data derived from Spanish IVF reports (SEF).

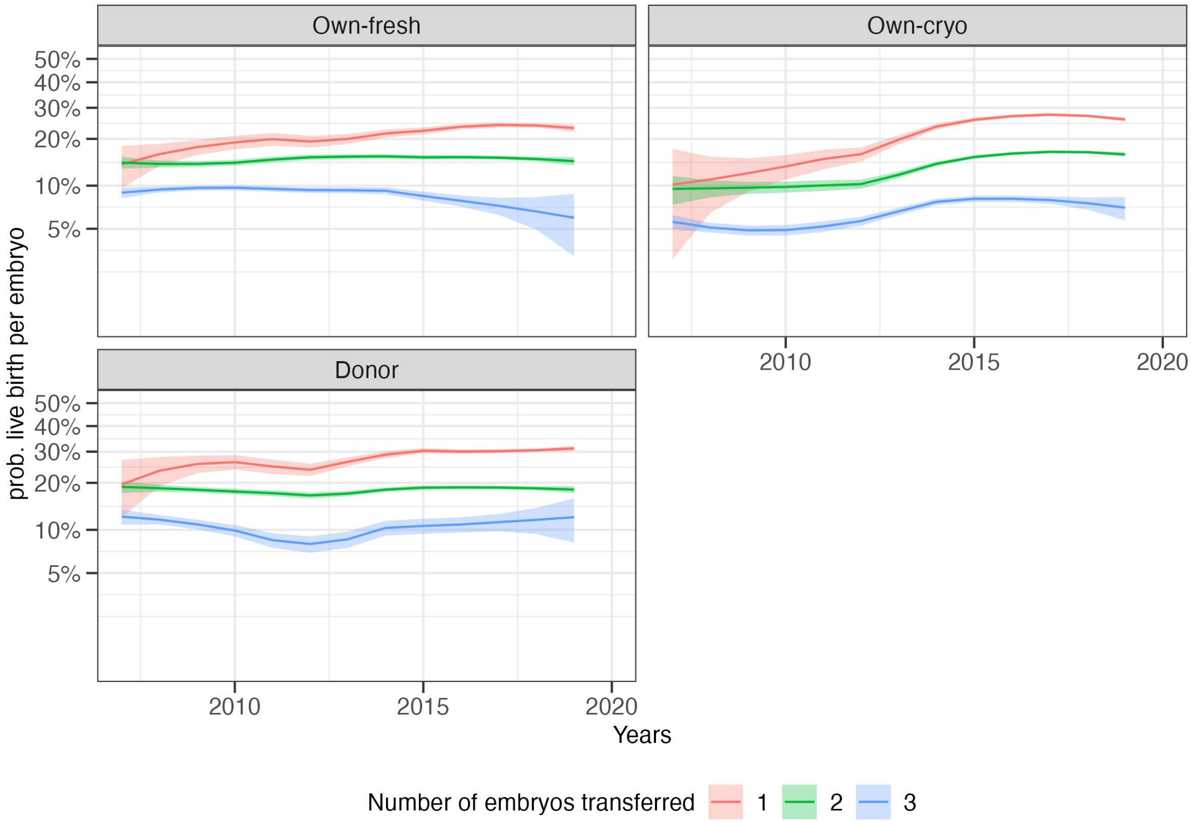
The probability of success per embryo is obtained by applying the binomial law, as explained in the text, and represented using a logistic scale. The series are smoothed with the Loess algorithm, with a span value of 0.75 (Cleveland & Grosse, 1991) using the numbers of deliveries as weights, which allows computing a 95% confidence interval for the curves (the region where 95% of the fitted curves obtained with similar sets of data would be found). Deliveries are corrected to include clinical pregnancies lost to follow up.

Figure 5-5. Probability of a live birth per embryo, according to the number of embryos transferred and the origin of eggs, UK for the period 1992-2018



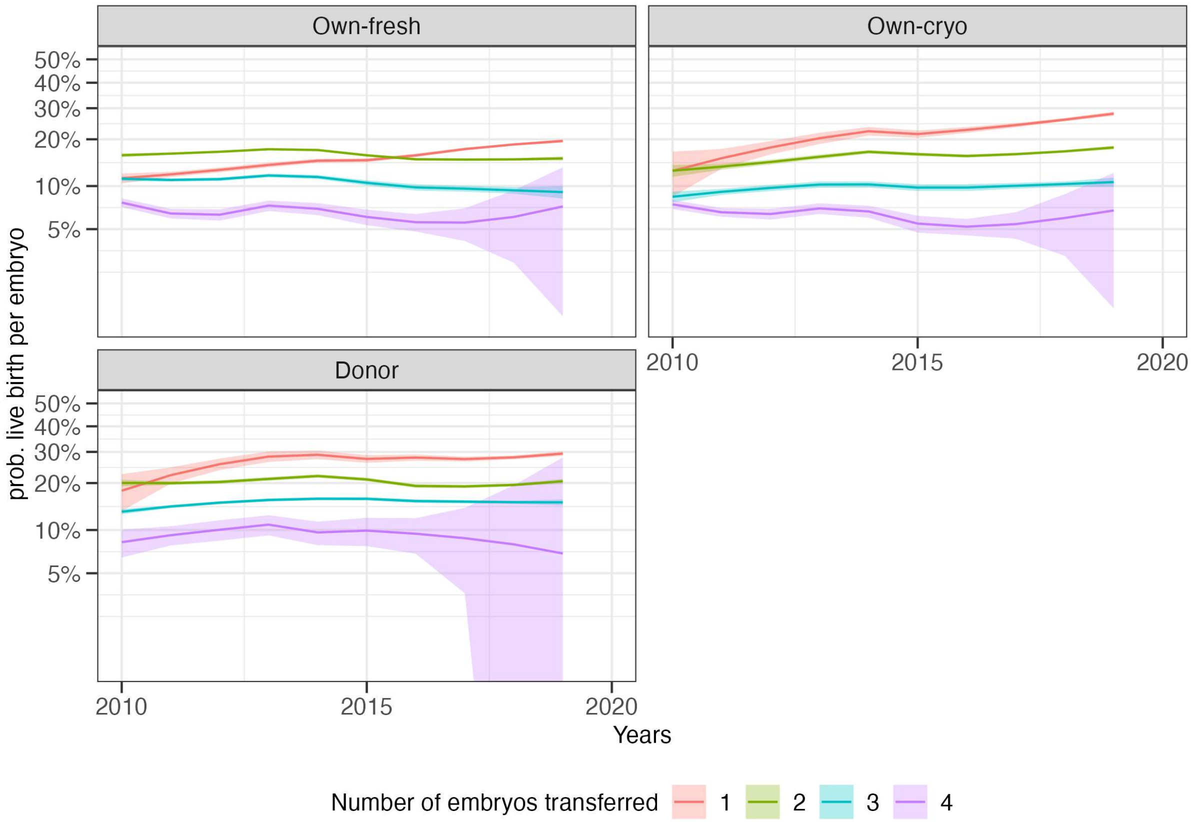
Data derived from UK registry microdata files (HFEA). The probability of success per embryo is obtained by applying the binomial law, as explained in the text. A logistic scale is used. The series are smoothed with the Loess algorithm, with a span value of 0.75 (Cleveland & Grosse, 1991) using the numbers of deliveries as weights, which allows computing a 95% confidence interval for the curves (the region where 95% of the fitted curves obtained with similar sets of data would be found). The numbers of transfers of 3 embryos for fresh and cryo donor eggs are too small for obtaining series for the whole time-span.

Figure 5-6. Probability of a live birth per embryo, according to the number of embryos transferred and the origin of eggs, Russia for the period 2004-2018



Source: Data from the Russian ART registry (RAHR). The probability of success per embryo is obtained by applying the binomial law, as explained in the text. A logistic scale is used. The series are smoothed with the Loess algorithm, with a span value of 0.75 (Cleveland & Grosse, 1991) using the numbers of deliveries as weights, which allows computing a 95% confidence interval for the curves (the region where 95% of the fitted curves obtained with similar sets of data would be found). Deliveries are corrected to include clinical pregnancies lost to follow up.

Figure 5-7. Probability of a live birth per embryo, according to the number of embryos transferred and the origin of eggs, Latin America for the period 2010-2016



Source: Data from international Latin American registry (REDLARA). The probability of success per embryo is obtained by applying the binomial law, as explained in the text. A logistic scale is used. The series are smoothed with the Loess algorithm, with a span value of 0.75 (Cleveland & Grosse, 1991) using the numbers of deliveries as weights, which allows computing a 95% confidence interval for the curves (the region where 95% of the fitted curves obtained with similar sets of data would be found).

5.3.5 Measuring the embryo synergy effect

Calculation of the probability of a live birth per embryo, as defined here, can also be used to measure the effect of collaboration between embryos, whereby the implantation and survival of an embryo increase the corresponding probabilities for the others transferred at the same time. This effect has been already detected with clinical data. Thus (Matorras et al. 2005) were able to measure this synergy effect for implantation thanks to their extension of the binomial model, using data for 1,835 embryo transfers. They estimated that, when a first embryo had implanted, the probability of implantation of the next one increased by 22%. Numerous other studies had also documented the existence of a synergy effect for embryo survival. Hence, when compared with a singleton pregnancy, miscarriage risk seems to be lower when multiple embryos have already implanted. For example, (Miró, Vidal, and Balasch 2012) observed from clinical data that embryo survival was higher in twin pregnancies: 83% (867 of 1,046) compared with 76% (881 of 1,159) in singleton pregnancies, a result similar to those for previous comparable studies cited in that paper.

By comparison with a situation of independence, this collaboration effect, operating either at the implantation stage or for the rest of the pregnancy, may therefore increase the number of live births for transfers of more than one embryo. We propose, here, to measure this collaboration or synergy effect by comparing the value of the probability of success per embryo, calculated indirectly by the binomial formula [5.1] for transfers of more than one embryo, with the value computed directly by dividing the number of live births by the number of embryos transferred, i.e., similar to the Implantation Rate (IR), for countries that publish the necessary data.

In a situation of independence between embryos, the direct and indirect calculations will give the same result: $p_n = IR_n$ (where n is the number of embryos transferred and IR is calculated from live births). On the one hand, with a synergy effect, we will have: $p_n < IR_n$. This is due to the fact that the binomial formula is the inverse of the probability of failure, i.e., when no embryo implants, which means in the absence of any synergy effect. On the other hand, IR will incorporate this effect, if it exists, because it only measures successes. This is what we observe with figure 5-8 for transfers of two embryos in Canada, Latin America, Spain, and the UK: the mean level of the probability of a live birth per embryo measured by IR_2 is around 15% higher than when measured by p_2, which is strong evidence for the existence of a synergy effect, and which is also, to our knowledge, the first measurement of this effect from aggregated data at the national level. The level of this effect is roughly comparable with the estimates made from clinical data. Hence, to refer again to (Matorras et al. 2005), the higher probability of 22% for the second embryo that implants translates into a mean synergy effect of 11% for the implantation of two embryos. If we combine this with (Miró et al. 2012), observations on the higher survival rate of twins during the pregnancy, compared to singletons, we arrive at a value close to 1.2 for the ratio IR_2/p_2, which was, in fact, the value observed for UK at the end of last century. For transfers of three embryos, the synergy effect again reached 30% in the UK in the 1990s, which is also compatible with the supposition of (Matorras et al. 2005) that the effect is cumulative, and seems to be double for the third embryo when two have already implanted. The level decreased sharply afterwards, especially for transfers of three embryos. This is obviously related to the increase in age of patients, although it is not clear from published clinical data whether it is because of a diminution of the collaboration effect at the implantation stage, or a reduction of the gap in miscarriage risks, although the latter seems to be the more probable cause.

Figure 5-8. Detecting and measuring the synergy effect: ratio of the probabilities of a live birth per embryo computed directly or indirectly, by IR_n/p_n, for transfers of 2 or 3 embryos with own fresh eggs

Fuente. Data derived from the Canadian ART register 2008-12 (CARTR), Latin America combined registers 2010-19 (REDLARA), Spanish IVF reports 2009-19 (SEF) and UK registry microdata files 2004-18 (HFEA).

The synergy effect is measured by the ratio of probabilities corresponding to the formula IR_n/p_n where IR_n is the total number of live births by the total number of embryos transferred and p_n is the probability as computed with the binomial formula, both for transfers of n embryos. As for Figure 5-4, the series are smoothed with the Loess algorithm, with a span value of 0.75, using the numbers of embryos as weights.

5.4 Discussion

The number of embryos transferred in each IVF cycle is a key variable for strategies to maximise the chances of obtaining a live birth while minimising the risk of a multiple birth. National ART registries have always proportioned series of transfers according to the number of embryos. However, they have been slow to incorporate data on the success of these treatments according to the number of embryos originally transferred, and not all national registries publish data on deliveries cross-classified by both the number of live births and the number of embryos transferred. The indirect calculation introduced in this article of the probability of success of each transferred embryo is therefore justified by the lack of more complete data that would allow direct calculation by simply dividing the number of live births by the number of transferred embryos. However, this also had a positive side because the need to use the indirect method allowed us to obtain a result we had not expected at the outset, which is measurement of the synergy effect when this probability can be calculated by both methods, direct and indirect. This may oblige the analyst to decide which of these two methods is more appropriate in the case where the necessary data are available. It seems to us that in most cases the indirect method should be chosen, because it is immediately compatible with LBR per number of embryos transferred, and would also allow calculation of a standardised LBR, with a constant composition of the number of embryos transferred, thus eliminating the effect of variation of this composition. Another reason for preferring the indirect method is, precisely, that it is more adequate for comparing the success of transfers according to the number of embryos, because it does not take into account the synergy effect, which represents a sort of bias when judging the success of treatments. On the other hand, use of the direct method is justified for measuring this effect specifically.

A significant limitation when calculating the probability of a live birth per embryo, especially when using the indirect method, is that it presupposes that this probability is the same for all transferred embryos, which is not only unrealistic, but is also contrary to the most recent clinical strategies, in which the transfer of several embryos is justified when one of them is of lower quality. In order to take this into account, it would be necessary to have individual data, case by case, with precise information, not only on the age of the patients, but also the quality of the embryos, the number of days of development before the transfer, and even the age of egg retrieval, in order to compare all types of cycles, with own or donated eggs, and with or without cryopreservation. Unfortunately, no national registry publishes microdata with this full type of detail.

Finally, although the precise factors that contribute to embryo synergy are still unclear, it is apparent that this phenomenon has a significant impact. Therefore, when deciding on the number of embryos to transfer, medical professionals should take it into account, particularly in younger women and when combining lower-quality embryos with higher-quality ones.

CAPÍTULO VI - Conclusiones

6.1 Resumen y discusión de resultados

Esta tesis doctoral ha analizado los mecanismos que explican el uso de las técnicas de reproducción asistida y ha evaluado sus impactos reproductivos, demográficos y sociales. A través de los análisis de la Encuesta de Fecundidad (2018), los informes de la Sociedad Española de Fertilidad e información estadística complementaria, se ha demostrado que actualmente el uso de las técnicas de reproducción asistida tiene un impacto notable en la natalidad en nuestra sociedad. A continuación, se resumen los resultados específicos de cada uno de los capítulos que componen la tesis y se discuten de forma conjunta.

Los resultados del Capítulo II indican que crece la cantidad de mujeres con estudios avanzados que llegan a cierta edad teniendo trabajo, nivel socioeconómico estable, pero no teniendo hijos. Por motivos biológicos es más difícil quedarse embarazada naturalmente a partir de 35 años. Los resultados también apuntan a que las nuevas generaciones se someten a los tratamientos con más frecuencia, ya que según la Encuesta de Fecundidad (2018) en España hay 14% de mujeres que apuntaron que tenían dificultades de concebir y utilizaban o no (pero necesitaban) los tratamientos TRA (8,9% de todas las mujeres). Concluimos que ello podría deberse al retraso en la maternidad, el desarrollo de la calidad de las mismas técnicas, los cambios en las formas de familia y los avances en la legislación.

En los Capítulos III y IV estimamos el efecto de las TRA sobre la natalidad a partir de datos del registro nacional español de reproducción asistida (SEF), considerando FIV/ICSI, IA y coito programado, y de la Encuesta de Fecundidad 2018. Mostramos que alrededor del 8% de los nacimientos en España en 2019 se debieron a tratamientos MAR, concretamente un 6,5% corresponden a FIV y 1,5% a IA y otros tratamientos. Es un nivel alto en comparación con otros países europeos, muy cerca de la cifra de Dinamarca, el país europeo con el nivel más alto. Esta estimación es inferior a la que se desprende de los registros debido a que se descontaron los ciclos (alrededor de un 35% del total) practicados a pacientes que residen y, por lo tanto, dan a luz en el extranjero.

Pero al mismo tiempo es una estimación que recupera los partos perdidos durante seguimiento (alrededor del 20% en la década de 2000 y del 10% en la década de 2010).

En el Capítulo IV mostramos además, utilizando un método de descomposición que mejora la estandarización directa, que el 80% de la variación en la multiplicidad de los partos es atribuible al uso de técnicas de reproducción asistida. Este resultado implica dar más importancia que antes al uso de estos tratamientos (que aumentan el riesgo de multiplicidad al transferir varios embriones para maximizar el éxito), en comparación con el aumento de la edad de la mujer en sí, que también está vinculado a la multiplicidad por al incremento de la hormona FHS en las edades de 35-39 años (Waterhouse, 1902).

Finalmente, en el Capítulo V se ha propuesto un nuevo indicador para medir el éxito de los tratamientos de reproducción asistida a partir del número de embriones transferidos. Este permite hacer comparaciones más precisas entre diversos países y diversos tipos de óvulos (frescos, congelados, propios o donantes). También detectamos y medimos el efecto de la sinergia embrionaria o el efecto de colaboración con datos de registros agregados.

Los resultados ponen en evidencia la particularidad del caso estudiado: España es líder en el uso de las técnicas a nivel europeo (segundo puesto después de Rusia en 2019 por los tratamientos realizados). Esta excepcionalidad se explica por una serie de elementos que configuran un marco favorable para la satisfacción de la demanda de asistencia: i) la creciente aceptación social de esta opción; ii) la legislación vigente (Ley 14/2006 de 26 de mayo de reproducción asistida de 2006) que universaliza su acceso y desarrolla el turismo reproductivo; iii) la importante cobertura por parte de la Sanidad pública del coste de los tratamientos; iv) amplia cobertura territorial por el país.

A pesar de este marco favorable para la reproducción asistida, constatamos que todavía existen desigualdades en el acceso a TRA en España. Hay grande parte de mujeres, que no se lo pueden permitir, mayormente, por cuestiones económicas. La Seguridad Social no cubre la donación, no cubre los tratamientos de las mujeres solteras, no cubre los tratamientos para mujeres mayores de 40 años (en Madrid, mayores de 45 años). Las colas para acceder a tratamientos por público todavía son largas y no todas las mujeres pueden permitir perder tiempo esperando ~~a~~ sus tratamientos. Los hombres homosexuales no pueden permitirse el acceso a las TRA, porque en España no se permite la maternidad subrogada.

El estudio del impacto de la reproducción asistida es de suma importancia en la actualidad. Muchas mujeres optan por obtener estudios, asegurar trabajos estables y encontrar a la pareja adecuada antes de considerar la maternidad. Sin embargo, surge el problema de que, con el paso de los años, muchas de ellas se enfrentan a dificultades para concebir a partir de los 35 años, lo que las lleva a buscar ayuda médica para lograr el embarazo. En este sentido, es importante destacar que muchos niños no habrían nacido sin el uso de las técnicas de reproducción asistida.

En los últimos años, se han producido avances significativos en las técnicas de reproducción asistida, lo que ha mejorado la tasa de éxito de los tratamientos y ha dado lugar al surgimiento de nuevas técnicas. Sin embargo, no se puede considerar que las técnicas de reproducción asistida sean una solución definitiva para la baja fecundidad. Lamentablemente, la eficacia de estos tratamientos todavía no alcanza el 100%, lo que implica que algunas mujeres nunca logren cumplir su deseo de ser madres.

6.2 Principales contribuciones de la tesis

En síntesis, esta tesis ofrece un análisis valioso de la reproducción asistida en España. Alcanza los objetivos de investigación planteados, analizando i) los cambios demográficos y sociales que han contribuido al aumento de la demanda de TRA; ii) las condiciones y pautas de acceso a los TRA; iii) los factores que determinan el éxito de los tratamientos; iv) los efectos reproductivos de las TRA y v) los efectos demográficos de las TRA. Así, se ha estimado la contribución de la reproducción asistida al número de nacimientos, se ha establecido en qué medida el aumento de los partos múltiples es debido al aumento de la edad materna y al uso de las TRA, se ha estimado la demanda potencial de tratamientos y se ha identificado y explicado el gradiente social en el acceso.

Estos resultados y la investigación llevada a cabo ofrecen una serie de contribuciones científicas (sustantivas y metodológicas), relevantes que se presentan a continuación:

- **Análisis de un fenómeno emergente:** se aborda el estudio de la reproducción asistida cuyas implicaciones, por su novedad y velocidad de transformación, están todavía poco exploradas.

- **Preguntas de gran relevancia demográfica y sociológica**: la investigación contribuye al debate científico y político-social entorno a dos grandes preguntas: la primera referida a las implicaciones demográficas: ¿en qué medida el uso de técnicas de reproducción asistida es un antídoto ante el retraso y la caída de la fecundidad?; y la segunda a las implicaciones sociales: ¿en qué medida existen desigualdades en el acceso a las técnicas de reproducción asistida en un marco regulador poco restrictivo?

- **Estudio de un caso excepcional:** el foco de la tesis en el caso de España permite entender los factores que explican la excepcional importancia de la reproducción asistida en España, contribuyendo así a entender de qué manera los factores contextuales (legales, demográficos y sociales) generan diferencias entre países en cuanto a reproducción asistida.

- **Uso combinado de distintas fuentes de información, de encuesta y de registro**: ante la escasez de datos por tratarse de un fenómeno emergente, la tesis hace una contribución decisiva combinando todos los datos disponibles y buscando de forma creativa la manera de comprender mejor el fenómeno. Trabajar combinando datos de registro y de encuesta, que tiene por definición particularidades distintas, supone siempre un reto en sí mismo y requieren de una madurez investigadora y de un dominio de las técnicas de análisis inherentes a cada dato.

- **Evaluación de la calidad de los datos**: Propuestas de mejora del registro de la SEF para mejorar las posibilidades de análisis demográfico y social, y recomendación de realizar una transición al acceso a datos individuales (debidamente anonimizados) y no agregados del registro. Contraste de datos de fuentes y naturaleza distinta.

- **Mejoras en la medición y propuesta de nuevos indicadores**. Esfuerzo por discutir los indicadores estándares y hacer una contribución metodológica que permita mejorar la medición de la incidencia, el éxito y el impacto de los tratamientos de reproducción asistida

- **Comparación internacional**: si bien la tesis analiza principalmente datos de España, se trabaja también con datos de otros países para ofrecer una visión comparada, siempre que esto sea posible.

6.3 Limitaciones y futuras líneas de investigación

Los resultados de esta investigación presentan algunas limitaciones, muy determinadas por las características de la información disponible. Una de las principales restricciones es que los informes estadísticos de reproducción asistida ofrecen información sólo a nivel agregado, con lo cual es imposible hacer el análisis más detallado. También se ha confirmado que hay muchos casos perdidos, con lo que no hay ningún seguimiento de todas las mujeres que se sometieron a tratamiento. Por otro lado, los datos retrospectivos de la Encuesta de Fecundidad de España (2018) no recogen de forma completa las historias de acceso y uso a la reproducción, de manera que algunas características de las mujeres solo las conocemos en el momento de la encuesta y no en el del tratamiento. En la medida en la que la información disponible mejore la investigación sobre reproducción asistida podrá dar un salto cualitativo. Algunas posibilidades que se contemplan son las siguientes:

- La **disponibilidad de datos individuales** y no agregados (prevista por la SEF para este mismo año 2023) ampliará las opciones de investigación. Se dispondrá de información más precisa sobre los tratamientos y las pacientes de las clínicas reproductivas. Con los nuevos datos y aplicando las metodologías utilizados en esta tesis doctoral se podrá hacer los análisis más detallados de la reproducción asistida: medir el éxito de tratamientos a partir de la edad de mujer, de números de embriones transferidos, multiplicidad, etc. Teniendo los micro datos de TRA se podrá analizar la edad de las mujeres no solamente al momento de la transferencia de embriones, pero también en el caso de la crio preservación la edad a la misma.

- La **disponibilidad de datos longitudinales** sobre las historias reproductivas de las mujeres, con información completa y detallada sobre infertilidad, abortos, intentos de embarazo y uso de reproducción asistida a lo largo de sus vidas (**perspectiva longitudinal)**, permitiría llevar a cabo análisis más complejos. Por ejemplo, relacionar las características y condiciones de la mujer en el momento de iniciar un tratamiento para conocer su efecto en la probabilidad de uso y de éxito.

- Complementar el análisis cuantitativo realizado con un **análisis cualitativo**. La realización de entrevistas en profundidad a las mujeres que se han sometido a tratamiento o que querrían hacerlo permitirá entender mejor la línea vital y los factores socioeconómicos en el momento de usar las técnicas y, además, las cuestiones psicológicas de las mujeres usuarios de TRA. Con estos datos se puede ver la información de las mujeres como su posición geográfica, su contexto familiar y social, su estado psicológico al momento de entrar al tratamiento, en el tratamiento y después del tratamiento, los motivos para seguir con el tratamiento o dejarlo.

- Analizar el papel de los **hombres**. Hay muy poca información sobre los hombres. Los informes SEF contienen solamente los datos si la causa de infertilidad era masculina y si los materiales genéticos son del marido o del donante. Pero no hay ninguna información sociodemográfica de hombres. La Encuesta de Fecundidad conlleva muy pocos casos de hombres, que no es representativo de hacer el análisis. En futuro sería interesante también complementar los estudios con los datos de hombres.

- Desarrollar el **análisis comparativo entre países:** sería importante seguir avanzando en la comparación de las pautas de uso y éxito de la reproducción asistida con el fin último de evaluar el impacto de los distintos marcos normativos de regulación de acceso y cobertura pública.

Por último, y más allá de la disponibilidad de datos y de las perspectivas metodológicas que puedan enriquecer el estudio de la reproducción asistida, será necesario abordar **cuestiones éticas**. Las nuevas técnicas ayudan a las mujeres a cumplir sus deseos de ser madres, cuando es difícil de conseguirlo de manera natural. A esto se suma la posibilidad de evitar los problemas genéticos de los bebés, en algunos lugares se permite elegir el sexo de los bebés y, sus características físicas. En varios países se permite el uso del vientre de alquiler. Así que las mujeres están cada vez más relajadas y atrasan más la edad de convertirse en madres. Esto nos lleva a preguntarnos ¿hasta dónde pueden y deben llegar los avances en la reproducción asistida?

CAPÍTULO VII. - Bibliografía

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Annex 1. Equivalence of Kitagawa (1955) and Horiuchi et al (2008) methods for the decomposition of the variation of a rate or a proportion, when the population is distributed by one characteristic like age (as is the case of total multiplicity)

The best way of measuring total multiplicity is as the proportion of multiple deliveries (and not as a proportion of births):

$$M = \frac{D^m}{D}$$

Multiple deliveries D^m are function of the age of mothers, so we can write them as:

$$D^m = \sum_x D_x^m$$

D_x^m are multiple deliveries of mothers of age x, which are functions both of multiplicity by age m_x and of D_x, the number of women having a delivery at that age:

$$D_x^m = m_x D_x$$

Summing up, total multiplicity can be written as:

$$M = \frac{\sum_x m_x D_x}{D} = \sum_x m_x d_x$$

where $d_x = \frac{D_x}{D}$ and $\sum_x d_x = 1$.

Kitagawa (1955) presented a decomposition method for the variation of rates, or of proportions, which are function of population characteristics like age, sex, or other social or biological constructs. Her aim was to obtain a decomposition in terms of additive main effects, without any interaction effect. Horiuchi et al. (2008) proposed a more general method for the decomposition of the changes of any indicator. We compare here both methods in the case of decomposition of the variation of a rate or proportion, when the population is distributed by only one characteristic, in this case, age of mothers.

Kitagawa's method

The variation of a proportion like total multiplicity can be measured between different populations, or for the same population over time, which is the case that interests us here. The problem can be written as follows:

$$\Delta M = \Delta\left(\sum_x m_x d_x\right) = \sum_x \Delta(m_x d_x)$$

This means that the variation over time of total multiplicity ΔM is equal to the sum of the variation of the products of multiplicity and of the proportion of deliveries, both by age of mothers. The variation of each product is equal to:

$$\Delta(m_x d_x) = (m_x + \Delta m_x)(d_x + \Delta d_x) - m_x d_x$$
$$= d_x \Delta m_x + m_x \Delta d_x + \Delta m_x \Delta d_x$$

where $d_x \Delta m_x$ and $m_x \Delta d_x$ are, respectively, the effect of the variation of multiplicity by age and of the age composition of deliveries, and $\Delta m_x \Delta d_x$ is the interaction effect.

Kitagawa's solution for dealing with the interaction effect was to allocate it equally between the two main effects:

$$\Delta(m_x d_x) = \left(d_x \Delta m_x + \frac{\Delta m_x \Delta d_x}{2}\right) + \left(m_x \Delta d_x + \frac{\Delta m_x \Delta d_x}{2}\right)$$

Which after factorisation simplifies to:

$$\Delta(m_x d_x) = \Delta m_x \overline{d_x} + \Delta d_x \overline{m_x} \qquad \textbf{\textit{[4.7]}}$$

where $\overline{d_x} = d_x + \frac{\Delta d_x}{2}$ is the mean, or the value at mid-point of the interval of variation of the age composition term, and in the same way $\overline{m_x}$ is the value at mean point of multiplicity by age.

If we sum by age the terms of equation, we obtain Kitagawa's formula [4.3] in the text.

Horiuchi et al.'s method

The main problem when decomposing the variation over time of an indicator which involves a product of factors or more complicated functional forms, is how to deal with interaction. If we use a continuous approach, there will be no interaction and we can apply the total differential formula (where d and ∂ are total and partial differentiation respectively and t is time):

$$\frac{df(x_1, \dots, x_p)}{dt} = \frac{dx_1}{dt}\frac{\partial f(\dots)}{\partial x_1} + \cdots + \frac{dx_p}{dt}\frac{\partial f(\dots)}{\partial x_p} \qquad \textbf{\textit{[4.8]}}$$

Applied to the decomposition of the variation of total multiplicity, that would give us:

$$\frac{d}{dt}\left(\sum_x m_x d_x\right) = \sum_x \frac{d}{dt}(m_x) d_x + \sum_x m_x \frac{d}{dt}(d_x)$$

The main difference between this formula and Kitagawa's as shown in [4.3] in the text is the existence of an interaction effect between the variation of m_x and the variation of d_x, and Kitagawa's solution was to allocate it equally between each factor, and thus to hide it. The solution of Horiuchi et al. is instead to try to eradicate the interaction effect first, before calculating the main effects. They propose to start dividing the interval of variation in *n* steps, using something akin to Archimedes' method of exhaustion: increasing the number of steps will make the interaction effect tend to zero. They propose to approximate continuous formula [4.8] with:

$$\Delta f(x_1, \ldots, x_p) = \sum_{i=1,n} \Delta f_i^1(x_1, \ldots, x_p) + \cdots + \sum_{i=1,n} \Delta f_i^p(x_1, \ldots, x_p)$$

With $\Delta f_i^k(x_1, \ldots, x_k, \ldots, x_p) = f(\bar{x}_1^i, \ldots, x_k^i, \ldots, \bar{x}_p^i) - f(\bar{x}_1^i, \ldots, x_k^{i-1}, \ldots, \bar{x}_p^i)$

The logic of this solution is to use numerical integration, keeping the functional form of the indicator unchanged and computing its variation for each of the n intervals, and for each variable, holding the rest of the variables constant at a value chosen at midpoint: $\bar{x}_{j\neq k}^i = g(x_{j\neq k}^{i-1}, x_{j\neq k}^i)$. This differs from a strict application of formula [4.8] for which we would need to actually carry out a partial derivation of the function for each variable. But the crux of this solution is the type of function $g(\ldots)$ used for obtaining the values of variables at midpoint for each interval. Horiuchi et al. propose at least two kinds, a linear or a log-linear function of time, depending on the functional form of the indicator. The log-linear function makes sense for indicators like life expectancy, when the functional form involves the exponential function, which is not the case for multiplicity, for which the linear interpolation of the variables in the interval is the most appropriate. This gives us the following:

$$\Delta M = \sum\nolimits_x \left\{ \sum_{i=1,n} \frac{\Delta m_x}{n} \bar{d}_x^i + \sum_{i=1,n} \bar{m}_x^i \frac{\Delta d_x}{n} \right\}$$

Where Δm_x and Δd_x are the variations of the two variables by age over the whole time-interval; $\Delta m_x/n$ and $\Delta d_x/n$ are their variation in each one of the *n* sub intervals; $\bar{m}_x^i = m_x^{i-1} + \left(\frac{\Delta m_x}{n}\right)/2$ and $\bar{d}_x^i = d_x^{i-1} + \left(\frac{\Delta d_x}{n}\right)/2$ are their values at midpoint of interval *i*.

For the MAR effect at age *x*, we have:

$$\frac{\Delta m_x}{n} \sum_{i=1,n} \left(d_x^0 + (i-1)\frac{\Delta d_x}{n} + \frac{\Delta d_x}{n}/2 \right) = \Delta m_x \bar{d}_x$$

This is the same result as that obtained with Kitagawa's method. Hence, we obtain the exact same decomposition of multiplicity with Kitagawa and Horiuchi et al. methods. This also gives a neat theoretical justification for Kitagawa's implicit hypothesis that the right way to obtain a decomposition without an interaction effect is to allocate it equally between the two main effects.

Note that the two methods give the same result only when the population is distributed by one characteristic. However, this will not be the case when two or more are combined, for example age, matrimonial status, employment status, etc. Kitagawa's method was extended later by Das Gupta (1991) to rates or proportions for populations classified by more than one characteristic, with the same objective of obtaining an exact decomposition into main effects, without any interaction effect. By contrast, the method of Horiuchi et al. (2008) will only provide an approximation of the total variation when there is more than one characteristic, albeit with very close results to the exact decomposition of Das Gupta.

Annex 2. National reports on MAR treatments used:

Belgium: *Assisted Reproductive Technology National Summary Reports*, years 1999-2018 https://www.belrap.be/Public/Reports.aspx.

Canada: Canadian Assisted Reproductive Technologies Register (CARTR), 2008-2017: https://cfas.ca/cgi/page.cgi/cartr-annual-reports.html

Catalonia: *FIVCAT.NET: estadística de la reproducció humana assistida a Catalunya*, years 2001-2014: https://scientiasalut.gencat.cat/handle/11351/987.

Denmark: *The Danish National Register of assisted reproductive technology* (in Danish), years 2000-2019: https://sundhedsdatastyrelsen.dk/da/registre-og-services/om-de-nationale-sundhedsregistre/graviditet-foedsler-og-boern/ivf-registeret.

Latin America: Red Latinoamericana de Reproducción Asistida (REDLARA), 2010-2019: https://redlara.com/

Other European countries: yearly ESHRE reports. The last one consulted is: *ART in Europe, 2017: results generated from European registries by ESHRE*, years 2001-2017: https://www.eshre.eu/Data-collection-and-research/Consortia/EIM/Publications.aspx

Portugal: Sociedade Portuguesa de Medicina da Reprodução (SPMR), 2009-2017: https://www.spmr.pt/pma

Russia: *ART Register Reports of the Russian Association of Human Reproduction* (RAHR in Russian), years 2002-2017: https://www.rahr.ru/registr_otchet.php

Spain: *Informes de la Sociedad Española de Fertilidad* (SEF), 1999-2019: https://www.registrosef.com/index.aspx#Anteriores.

Statistics Korea. (2019). *Final Results of Birth Statistics in 2018 (Press Release)*.

Switzerland: *Swiss Society for Reproductive Medicine*, years 2006-2012: https://sgrm.org

United Kingdom - *Human Fertilisation and Embryology Authority* (HFEA) register, 2001-2017: https://www.hfea.gov.uk/about-us/data-research/

USA: Centers for Disease Control and Prevention (CDC) *Assisted Reproductive Technology Reports*, years 2001-2017: https://www.cdc.gov/art/artdata/index.html

Last access to all these registers was made in December 2022.

Annex 3. Glosario

Criopreservación: conservación de gametos/tejidos para su futura utilización en diferentes tratamientos de reproducción asistida. Es la técnica más popular en la preservación de la fertilidad.

Coito programado: técnica básica de reproducción asistida que consiste en localizar el momento más fértil de la mujer e indicar relaciones sexuales dirigidas. Se puede hacer con o sin inducción de la ovulación (medicación) y bajo el control ecográfico, analítico o temporal.

Donación de gametos (óvulos, espermatozoides, embriones): técnica de reproducción asistida que emplea gametos de un tercero para conseguir una gestación en un paciente que requiere el uso de gametos de un donante.

Donante de ovocitos: mujer que dona sus ovocitos con fines reproductivos a otra mujer que los necesite. En España se rige bajo los preceptos de la ley de reproducción asistida, bajo la premisa del anonimato.

Donante de semen: varón que dona sus espermatozoides, bajo la premisa del anonimato de acuerdo a la ley vigente en España, con el objetivo de que una mujer o pareja hagan un tratamiento de reproducción asistida.

Embrión: conjunto celular que da lugar a la unión de un ovocito y un espermatozoide, cuya correcta evolución dará lugar a un recién nacido vivo.

Esterilidad: incapacidad de conseguir una gestación a pesar de mantener relaciones sexuales continuadas sin protección anticonceptiva durante más de 12 meses en mujeres menores de 35 y 6 meses en mujeres mayores de 35 años.

Fertilidad: capacidad para reproducirse o procrear.

Fecundidad: el estudio de la frecuencia de los nacimientos vivos, por edad de la madre, en relación con las mujeres en edad de procrear (15-49).

Fecundación/Fertilización: activación del ovocito por el espermatozoide. Un óvulo correctamente fecundado presentará 2 pronúcleos y 2 corpúsculos polares, al día siguiente de la fecundación in vitro.

FIV: Fecundación In Vitro. Técnica de laboratorio en la que se fertilizan los ovocitos con semen en una placa de Petri. En la técnica clásica la fecundación se da de manera espontánea, los gametos comparten placa y se fecunda el óvulo sin que el técnico del laboratorio interceda. En la ICSI el técnico de laboratorio fertiliza el óvulo mediante una microinyección espermática.

FSH: hormona folículo estimulante. Puede ser endógena (producida por la hipófisis) o farmacológica (recombinante o urinaria) y forman parte de los protocolos de estimulación de los ovarios en los tratamientos de reproducción asistida.

Infertilidad: incapacidad para conseguir un recién nacido.

ICSI: inyección intracitoplasmática de espermatozoides: técnica de reproducción asistida en la que se fuerza la fecundación en el laboratorio mediante la microinyección de un espermatozoide seleccionado en el citoplasma de un ovocito obtenido tras una punción ovárica.

Inseminación artificial (IAC, IAD): técnica de reproducción asistida en la que se depositan espermatozoides (de pareja o de banco) en el interior del útero de una paciente en el momento de ovulación programada.

Ovocito: también llamado óvulo. Es el gameto femenino. Se encuentra dentro del folículo, en el ovario. Cuando está maduro (metafase II) puede ser fecundado y dar lugar a un embrión.

Subrogación uterina: es una técnica mediante la cual el útero de una mujer gesta el embrión de otra. La ley española no recoge esta técnica en su ordenamiento jurídico.

Técnicas de Reproducción Asistida (TRA): conjunto de técnicas de laboratorio y tratamientos médicos que tienen como objetivo conseguir un embarazo. Las más habituales son la inseminación artificial (IA) y la Fecundación In Vitro (FIV) con sus variantes. En esta última, tras la obtención de los gametos masculinos y femeninos, se procede a la fecundación en el laboratorio para conseguir un embrión que será transferido al útero para que implante.

Fuente. Sociedad Española de Fertilidad, SEF