Trends in clomiphene citrate and gonadotropins use in women with infertility between 2010 and 2017: A population-based study in France

Bastien Bourrion, Henri Panjo, Mathilde François, Nathalie Pelletier-Fleury

Received: 24 May 2022 | Revised: 31 January 2023 | Accepted: 16 March 2023

DOI: 10.1002/pds.5616

ORIGINAL ARTICLE

WILEY

Trends in clomiphene citrate and gonadotropins use in women with infertility between 2010 and 2017: A population-based study in France

Bastien Bourrion[1,2] | Henri Panjo[1] | Mathilde François[1,2] | Nathalie Pelletier-Fleury[1]

[1]INSERM, Université Paris-Saclay, UVSQ, CESP, bâtiment 15/16 Inserm, Hôpital Paul Brousse, 16 Avenue Paul Vaillant Couturier, 94807 Villejuif Cedex, France

[2]Département de Médecine Générale, UVSQ, Faculté des Sciences de la Santé Simone Veil, Montigny le Bretonneux, France

Correspondence
Bastien Bourrion, Département de Médecine Générale, 2 Avenue de la Source de la Bièvre, 78180 Montigny le Bretonneux, France.
Email: bastien.bourrion@inserm.fr

Funding information
Agence Nationale de la Recherche, Grant/Award Number: ANR-17-CE36-0011-01

Abstract

Purpose: To describe temporal trends and assess factors associated with changes in the prescription of clomiphene citrate and gonadotropins between 2010 and 2017 in women with infertility aged 18–50 from metropolitan France.

Methods: 6321 prevalent women from a representative sample of the national medico-administrative database were identified. We performed a Cochran-Armitage trend test and calculated the rate ratios. A Poisson regression was used to derive the incidence rate ratios, for each treatment class.

Results: The prevalence rate and incidence rate of clomiphene citrate use significantly decreased by 20% (RR 0.80: 95% CI 0.71–0.90) and 23% (RR 0.77: 95% CI 0.66–0.89), respectively. Its initiation was higher in all age groups compared to the reference (18–24 years), with a downward gradient. It was also higher when the density of gynaecologists was higher and in disadvantaged areas. The prevalence rate and incidence rate of gonadotropin use increased by 11% (RR 1.11: 95% CI 1.01–1.22) and 33% (RR 1.33: 95% CI 1.14–1.55) respectively. Gonadotropin initiation was highest in the 31–35 age group, but it was also higher in the 25–30 and 36–40 age groups at a similar level (reference 18–24 years). Its initiation was higher when the density of gynaecologists was higher, but not associated with social deprivation.

Conclusion: Our results showed an increase in gonadotropin use for infertility treatment in France during the 2010–2017 period and a decrease in clomiphene citrate use. Further work should be undertaken to analyse the use of these drugs in relation to women's care pathways.

KEYWORDS
clomiphene citrate, gonadotropins, infertility, pharmacoepidemiology

Key Points

- The prevalence and incidence rates of clomiphene citrate use decreased significantly by 20% (RR 0.80: 95% CI 0.71–0.90) and 23% (RR 0.77: 95% CI 0.66–0.89) respectively. This decrease in incidence rate could be related to the decrease in clomiphene citrate use in 18–24 and 25–35 age groups.

- The prevalence and incidence rates of gonadotropin use increased by 11% (RR 1.11: 95% CI 1.01–1.22) and 33% (RR 1.33: 95% CI 1.14–1.55) respectively. This increase in incidence rate was related to a large increase in gonadotropin use in 31–35 and 36–40 age groups.
- A high density of gynaecologists is associated with higher initiation.
- Gonadotropin initiation was the highest in the 31–35 age group (reference 18–24 years), but it was also higher in the 25–30 and 36–40 age groups at similar level.
- The initiation of clomiphene citrate was associated with disadvantaged areas.

Plain Language Summary

The objective of this study was to describe temporal trends and factors associated with changes in the prescription of the two main infertility treatments, clomiphene citrate and gonadotropins. This study was conducted between 2010 and 2017 on a representative sample of 1/97th of French women aged 18–50. 6321 prevalent women were identified of whom 3212 had at least one clomiphene citrate dispensation, and 3922 women had at least one gonadotropin dispensation. Clomiphene citrate and gonadotropins treatments were initiated by 2818 and 2599 women, respectively. The prevalence rate and the number of new women using clomiphene citrate decreased significantly by 20% and 23%, respectively, especially among women aged 18–35 years. The prevalence rate and the number of new women using gonadotropins increased significantly by 11% and 33%, respectively, especially among women aged 31–40. Regardless of the type of drug, the probability of prescription increased with the number of gynaecologists. Social disadvantage was associated with increased clomiphene citrate initiation. Further studies should be carried out to analyse the evolution of these different prescriptions according to the type of care pathway.

1 | INTRODUCTION

Globally, the age-standardised prevalence rate of infertility increased by 0.37% per year in females between 1990 and 2017.[1] In Europe, the use of assisted reproductive technology (ART) treatment increased by 2.4% between 2016 and 2017, leading to a 1.2% increase in ART-related births.[2] Social-demographic changes (longer periods of study, difficulties in obtaining stable employment, children from a second union, etc.) and a high exposure to risk factors (tobacco, obesity, alcohol, etc.) are the cause of this.[3] It has recently been shown that 1.25% of women aged 20–49 in France are treated for infertility each year.[4] The use of infertility treatment increased by 23.9% amongst women aged 34 and over, although it remained stable amongst those under 34.

Infertility places a significant burden on individuals and communities. Quality of life and emotional status are affected by infertility care.[5] The economic burden is also high, largely due to ART techniques.[6] A study in France recently analysed the size and distribution of expenditure related to infertility treatment over time, and estimated the economic burden of infertility treatment in France.[7] One of the main results, in addition to quantifying the economic burden of infertility management (estimated at 6996 [95% CI: 5755–8237] euros over a 3.5-year follow-up period), was demonstrating the significant share of health care expenses related to drugs, especially in the first two semesters of infertility management (47% and 35% of expenses, respectively).

Two main classes of molecules were involved in the treatment of infertility: clomiphene citrate and gonadotropins. Clomiphene citrate is indicated for the treatment of infertility due to anovulation and normogonadotropic, normoprolactinemic anovulation.[8] Gonadotropins are indicated in cases of amenorrhoea not responding to progestin testing; failure of, or intolerance to, clomiphene citrate; and for ovulation stimulation and insemination, and in vitro fertilisation (IVF).

Until now, two studies have examined the use of drug treatment for infertility.[9,10] These studies showed a decrease in the prevalence rate of clomiphene citrate use. The rate remained stable in one of the studies.[10] To our knowledge, no one has yet analysed the evolution of clomiphene citrate and gonadotropin prescriptions in terms of volume over time, according to socio-demographics and supply characteristics.

Given the social-demographic changes and the epidemiological context described above, we hypothesised an increase in the volume of clomiphene citrate and gonadotrophins used. Based on the literature, there may be a decrease in the use of clomiphene citrate.

The primary objective of this study was, therefore, to describe changes in the use of the two main classes of drugs used to treat infertility. The secondary objective was to assess the factors associated with the initiation of treatment with these drugs.

2 | METHODS

2.1 | Database

The study was based on the Permanent Beneficiaries Sample (Echantillon Généraliste de Bénéficiaires, EGB), which is a French

medico-administrative database containing a 1/97 representative sample of the National Health Insurance Inter-Scheme Information System (Système National d'Information Inter-Régimes de l'Assurance Maladie, SNIIRAM), covering 98% of the French population.[11] The EGB is representative of the French population in terms of age and gender, and contains data for more than 660 000 people, whether they use healthcare or not. We used data for individuals affiliated to the main French health insurance scheme (general scheme, covering 76% of the French population), which has been stored since 2006. It contains information on the socio-demographic characteristics and healthcare use of the beneficiaries. The socio-demographic variables available are date of birth, gender, and postal code of residence. The EGB contains information relating to consultations, technical acts, and drugs dispensation with the date of completion, the amount reimbursed, and the healthcare professional who performed the procedure. Drugs can be identified by their Presentation Identification Code (Code Identifiant de Présentation—CIP) and their corresponding Anatomical Therapeutic Chemical (ATC) code. The CIP is a unique number for a given drug according to its packaging. It also contains information about the chronic conditions (Affection de Longue Durée—ALD) of beneficiaries. The ALDs are particularly costly and/or serious illnesses which entitle the beneficiaries to 100% reimbursement, for at least 5 years after their registration in the case of cancer. The EGB is linked to the private and public hospital discharge database (Programme de Médicalisation des Systèmes d'Information—PMSI), which is a medico-administrative database of public and private hospital stays. The PMSI contains, in particular, information on the main and associated diagnoses recorded during hospitalisation, and the date of admission and discharge.

ALDs and reasons for hospitalisations can be identified using the tenth version of the International Classification of Diseases (ICD-10).

2.2 | Population

2.2.1 | Prevalent cases

Prevalent cases in mainland France—women aged 18–50 affiliated to the general scheme—were identified each year between 2010 and 2017, according to whether they had at least one purchase of clomiphene citrate or gonadotropins (see Supplemental Table 1 for the list of drugs). Because drugs for infertility can also be used in the management of cancer and fertility preservation, women who had a chronic condition (cancer), or were hospitalised with a cancer diagnosis were excluded in the year of declaration and/or hospitalisation.

2.2.2 | Incidental cases

Incidental cases in mainland France—women aged 18–50 affiliated to the general scheme—were identified between 2010 and 2017, if they had at least one purchase of clomiphene citrate or gonadotropins in the year of inclusion, on the condition that they had not used these drugs in the 3 years prior to their inclusion (see Supplemental Table 1). Because drugs for infertility can be used in the management of cancer and fertility preservation, women who had a chronic condition (cancer) or were hospitalised with a cancer diagnosis were excluded in the year of declaration and/or hospitalisation.

2.3 | Variables

The variables of interest were age in six categories, year (from 2010 to 2017), Social Deprivation Index terciles (Indice de Désavantage Social—FDEP13), and the terciles of the Local Potential Accessibility to gynaecologists (Accessibilité Potentielle Localisée—APL), calculated in 2013.[12,13] The French Deprivation Index (Fep13) is an ecological measure that characterises the socio-economic status of an individual based on their postcode of residence. It is defined at the postcode level as the first component of a principal component analysis of the following four variables: median household income, the percentage of graduates in the population over 15 years old, the percentage of workers in the active population, and the unemployment rate. The APL is a local indicator calculated in 2013, available at the postcode level, which takes into account supply and demand from surrounding municipalities. It highlights disparities in health care supply, which a conventional density indicator, calculated on a much wider scale, tends to mask. The APL takes into account the level of activity of practicing professionals as well as the age structure of the population in each municipality, which affect health care needs. The calculation of the APL takes into account: private gynaecologists' practices, including secondary practices; their activity recorded in full time equivalents estimated from the number of procedures performed during the year; and an estimation of the declining use of gynaecological care at a distance between 0 and 45 min (thresholds at 15, 30, and 45 min) from the practices. It is defined in full-time equivalent per 100 000 inhabitants.

2.4 | Analyses

2.4.1 | Prevalence rate analyses

We performed a descriptive analysis of the prevalence rate per 1000 women by age group according to the year for each treatment class (clomiphene citrate and gonadotropins). We performed a Cochran-Armitage trend test to analyse the evolution of the prevalence rate over time, and calculated the rate ratio, and the 95% confidence interval between 2010 and 2017.

2.4.2 | Incidence rate analyses

First, for each treatment class (clomiphene citrate and gonadotropins), we performed a descriptive analysis of the incidence rate per 1000 women by year, age group, and by age group according to the year. We performed a Cochran-Armitage trend test and calculated the rate

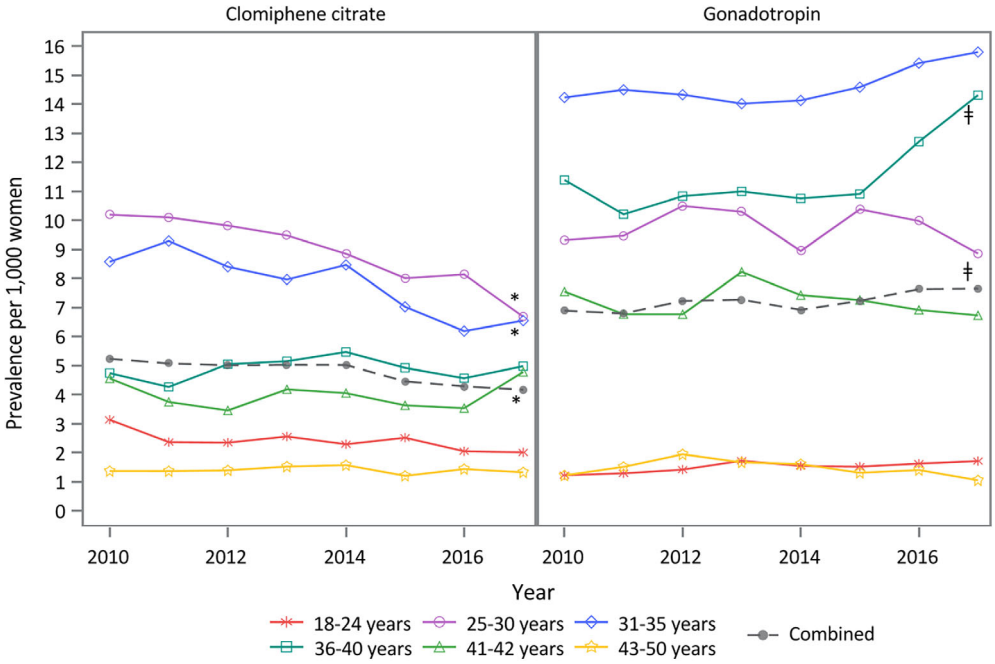

FIGURE 1 Evolution of the prevalence rate of clomiphene citrate and gonadotropin use per 1000 women by age group according to the year.

ratio, and the 95% confidence interval between the year 2010 and the year 2017, to analyse the evolution of the incidence rate over time.

A Poisson regression was then used for each treatment class to derive the incidence rate ratios adjusted for age in six categories (25–30, 31–35, 36–40, 41–42, and 43–50, vs. 18–24), APL in three categories (low, middle, and high), FDEP13 in three categories (advantaged, intermediate, and disadvantaged) corresponding to the terciles, and for the year of inclusion (from 2010 to 2017). We used the GENMOD SAS 9.4 procedure. Tests were performed with a two-sided alpha risk of 5%.

2.5 | Ethics

Access to the EGB (pseudonymous data) is subject to prior training and authorisation. The EGB was approved by the French National Commission for Data Protection and Liberties (Commission Nationale de l'Informatique et des Libertés, CNIL).

3 | RESULTS

3.1 | Prevalence rate

We identified a total of 6321 women between 2010 and 2017 aged 18–50, of whom 3212 had at least one clomiphene citrate purchase; 3922 women had at least one gonadotropin purchase. Amongst these women, 813 had purchased both classes.

The 1-year prevalence rate for clomiphene citrate use decreased significantly from 5.23 users per 1000 women in 2010 to 4.16 users per 1000 women in 2017 (rate ratio [RR] 0.80, 95% CI 0.71–0.90, $p < 0.0001$) (see Supplemental Table 2). This was related to a decrease in the prevalence rate of clomiphene citrate use by 34% ($p < 0.0001$) and 23% ($p < 0.0001$) in the 25–30 and 31–35 age groups respectively (see Figure 1).

The 1-year prevalence rate for gonadotropin use increased significantly from 6.89 users per 1000 women in 2010 to 7.65 users per 1000 women in 2017 (RR 1.11, 95% CI 1.01–1.22, $p < 0.006$) (see Supplemental Table 2). This was related to a 25% increase in the prevalence rate of gonadotropin use ($p < 0.0015$) in the 36–40 age group (see Figure 1).

3.2 | Incidence

Clomiphene citrate treatment was initiated by 2818 women between 2010 and 2017. The incidence rate of clomiphene citrate use was higher in the 25–30 (6.63 per 1000 women) and 31–35 age groups (5.18 per 1000 women). The incidence rate of clomiphene citrate use decreased significantly across all ages between 2010 and 2017, from 3.56 to 2.73 per 1000 women (RR 0.77, 95% CI 0.66–0.89, $p < 0.0001$) (see Table 1). This decrease could be related to the decrease in incidence rate of clomiphene citrate use in the 18–24 (RR 0.55, 95% CI 0.33–0.91, $p = 0.045$) and 25–35 age groups (RR 0.62, 95% CI 0.49–0.8, $p < 0.0001$), from 2.39 to 1.30 per 1000 women and from 7.56 to 4.72 per 1000 women, respectively. A non-linear significant downward trend was observed in the 31–35 (RR 0.78: 95% CI 0.59–1.05; $p = 0.0041$) age group.

TABLE 1 Incidence rate of clomiphene citrate and gonadotrophin use per 1000 women between 2010 and 2017.

		18–24	25–30	31–35	36–40	41–42	43–50	All
Clomiphen citrate	2010	2.39	7.56	5.95	2.83	2.42	0.66	3.56
	2011	1.88	7.92	6.40	2.93	2.46	0.66	3.63
	2012	2.29	7.80	4.87	3.08	2.50	1.10	3.58
	2013	2.06	6.94	5.08	3.58	2.60	0.88	3.45
	2014	2.18	6.85	5.72	3.67	2.07	0.94	3.56
	2015	2.05	5.26	4.75	3.27	2.73	0.32	2.90
	2016	1.75	6.10	4.02	2.92	1.98	0.64	2.89
	2017	1.30	4.72	4.67	2.79	3.28	0.71	2.73
	2010–2017	2.00	6.63	5.18	3.13	2.50	0.74	3.29
	RR[a]	0.55	0.62	0.78	0.98	1.36	1.07	0.77
	95% CI	(0.33–0.91)	(0.49–0.80)	(0.59–1.05)	(0.66–1.46)	(0.72–2.57)	(0.57–2.03)	(0.66–0.89)
	p value[b]	0.045	<0.0001	0.0041	0.9295	0.6515	0.3276	<0.0001
Gonadotropin	2010	0.64	4.00	5.48	3.49	2.56	0.41	2.57
	2011	0.65	4.58	5.56	4.00	2.89	0.44	2.80
	2012	1.04	5.48	5.64	4.12	3.06	0.55	3.12
	2013	1.11	4.48	6.29	4.30	3.28	0.44	3.06
	2014	0.75	4.18	5.04	4.84	2.48	0.61	2.82
	2015	0.94	4.93	7.04	4.13	2.58	0.43	3.18
	2016	0.91	5.06	6.84	5.10	2.28	0.43	3.31
	2017	1.07	3.83	8.07	5.81	2.97	0.29	3.41
	2010–2017	0.88	4.56	6.25	4.46	2.77	0.45	3.03
	RR	1.67	0.96	1.47	1.67	1.16	0.70	1.33
	95% CI	(0.81–3.47)	(0.71–1.30)	(1.13–1.92)	(1.22–2.28)	(0.61–2.21)	(0.28–1.75)	(1.14–1.55)
	p value[b]	0.1991	0.8992	0.0004	0.0007	0.7613	0.4932	0.0001

Note: Reading grid: In 2013, the incidence rate of clomiphene citrate use (all ages) was 3.45 per 1000 women, and the highest incidence rate of clomiphene citrate use was in the 25–30 age group (6.94 per 1000 women). For all years the incidence rate of clomiphene citrate use in the 25–30 age group was 6.63 per 1000 women. Between 2010 and 2017, in the 25–30 age group, the incidence rate of clomiphene citrate use decreased in a significant statistically linear way by 38% (RR 0.62, $p < 0.0001$).

[a]Rate ratio 2017 versus 2010; 95% CI = 95% confidence interval.

[b]The Cochran-Armitage test for linear trend.

Gonadotropin treatment was initiated by 2599 women between 2010 and 2017. The incidence rate of gonadotropin use increased significantly between 2010 and 2017 (RR 1.33: 95% CI 1.14–1.55, $p = 0.0001$). The increase in the incidence rate could be related to a large increase in gonadotropin use in the 31–35 (RR 1.47, 95% CI 1.13–1.92, $p = 0.0004$) and 36–40 age groups (RR 1.67, 95% CI 1.22–2.28, $p = 0.0007$), from 5.48 to 8.07 per 1000 women and from 3.49 to 5.81 per 1000 women, respectively.

In multivariate analysis, all things being equal, clomiphene citrate initiation was the highest in the 25–30 age group (reference 18–24 years) (adjusted rate ratio [ARR] 3.26, 95% CI 2.85–3.72, $p < 0.001$), although higher in all age groups compared to the reference, with a downward gradient and when the density of gynaecologists was higher (reference low density) (ARR 1.15, 95% CI 1.04–1.27, $p = 0.01$). It decreased from year 2015 (ARR 0.84, 95% CI 0.72–0.98, $p = 0.02$), compared to 2010 (reference), and more so in 2017 (ARR 0.79, 95% CI 0.68–0.92; $p = 0.003$), although 2016 was at the limit of statistical significance. Compared to the intermediate advantaged tercile of the FDEP (reference), clomiphene citrate initiation was higher in the disadvantaged tercile (ARR 1.20, 95% CI 1.08–1.32, $p < 0.0001$) and lower in the advantaged tercile (ARR 0.90, 95% CI 0.82–0.99, $p = 0.02$) (see Table 2).

In multivariate analysis, the gonadotropin initiation was the highest in the 31–35 age group (reference 18–24 years) (adjusted rate ratio [ARR] 5.98, 95% CI 4.95–7.23, $p < 0.001$), but it was also higher in the 25–30 (adjusted rate ratio [ARR] 4.40, 95% CI 3.64–5.33, $p < 0.001$) and 36–40 age groups (adjusted rate ratio [ARR] 4.25, 95% CI 3.50–5.17, $p < 0.001$) at a similar level. Gonadotropin initiation was higher when the density of gynaecologists was higher (ARR of the last tercile 1.15, 95% CI 1.03–1.28, $p = 0.01$). It increased from 2012 (ARR 1.24, 95% CI 1.06–1.46, $p = 0.01$), compared to 2010 (reference), and more so in 2017 (adjusted rate ratio [ARR] 1.33, 95% CI 1.13–1.56, $p = 0.001$), although 2014 was not significant. Unlike clomiphene citrate, the initiation of gonadotrophins was not associated with FDEP (see Table 3).

TABLE 2 Rate ratio and 95% confidence intervals of the incidence rate of clomiphene citrate use.

Variables		Number of clomiphene citrate users (*n*)	Incidence rate per 1000 women (95% CI)	Unadjusted rate ratio (95% CI)	Adjusted rate ratio[a] (95% CI)	*p*-value
Age group	18–24	278	2.06 (1.83–2.32)	Ref.[b]	Ref.	
	25-30	1087	6.59 (6.21–6.99)	3.20 (2.81–3.65)	3.26 (2.85–3.72)	<0.0001
	31–35	697	5.17 (4.80–5.57)	2.51 (2.19–2.89)	2.55 (2.22–2.93)	<0.0001
	36–40	413	3.1 (2.82–3.41)	1.51 (1.29–1.75)	1.52 (1.31–1.77)	<0.0001
	41–42	136	3.03 (2.57–3.59)	1.47 (1.20–1.81)	1.47 (1.20–1.80)	0.0002
	43–50	158	0.89 (0.76–1.04)	0.43 (0.35–0.52)	0.43 (0.36–0.53)	<0.0001
APL	Low density	490	3.44 (3.15–3.76)	Ref.	Ref.	
	Middle density	673	3.27 (3.04–3.53)	0.95 (0.85–1.07)	1.01 (0.90–1.13)	0.90
	High density	1606	3.63 (3.45–3.81)	1.05 (0.95–1.17)	1.15 (1.04–1.27)	0.01
Year	2010	370	3.61 (3.26–4.00)	Ref.	Ref.	
	2011	382	4.04 (3.65–4.46)	1.12 (0.97–1.29)	1.05 (0.91–1.22)	0.48
	2012	377	3.61 (3.26–4.00)	1.00 (0.87–1.15)	1.02 (0.89–1.18)	0.76
	2013	364	3.62 (3.26–4.01)	1.00 (0.87–1.16)	0.99 (0.86–1.14)	0.87
	2014	376	3.64 (3.29–4.02)	1.01 (0.87–1.16)	1.01 (0.87–1.16)	0.90
	2015	305	3.22 (2.88–3.60)	0.89 (0.77–1.04)	0.84 (0.72–0.98)	0.02
	2016	304	3.29 (2.94–3.68)	0.91 (0.78–1.06)	0.87 (0.75–1.01)	0.07
	2017	291	2.97 (2.64–3.33)	0.82 (0.70–0.96)	0.79 (0.68–0.92)	0.003
FDEP	Advantaged	1151	3.16 (2.98–3.35)	0.89 (0.81–0.98)	0.90 (0.82–0.99)	0.02
	Intermediate	718	3.54 (3.29–3.81)	Ref.	Ref.	
	Disadvantaged	900	4.02 (3.76–4.29)	1.13 (1.03–1.25)	1.20 (1.08–1.32)	<0.0001

Note: Forty-nine women who had used clomiphene citrate (1.7%) with a missing postcode were excluded. APL: tercile of the Local Potential Accessibility (Accessibilité potentielle localisée) to gynaecologist measures the spatial adequacy between supply and demand for care at the city level. FDEP: tercile of Social Deprivation Index (Indice de Désavantage Social) is an ecological measure that characterises the socio-economic environment in which individuals in a given geographic area live at a given time, based on the percentage of workers in the labour force, the percentage of high school graduates aged 15 and over, the percentage of unemployed in the labour force, and median household income.

[a]Adjusted rate ratio based on Poisson regression model including age group, Local Potential Accessibility to gynaecologists (APL), year, and Social Deprivation Index (FDEP).

[b]Ref. = reference category.

TABLE 3 Rate ratio and 95% confidence intervals of the incidence rate of gonadotropin use.

Variables		Number of gonadotropin users (*n*)	Incidence rate rate per 1000 women (95% CI)	Unadjusted rate ratio (95% CI)	Adjusted rate ratio[a] (95% CI)	*p*-value
Age group	18–24	123	1.04 (0.87–1.24)	Ref.[b]	Ref.	
	25-30	751	4.55 (4.24–4.89)	4.38 (3.62–5.30)	4.40 (3.64–5.33)	<0.0001
	31–35	848	6.18 (5.78–6.61)	5.95 (4.92–7.18)	5.98 (4.95–7.23)	<0.0001
	36–40	593	4.37 (4.04–4.74)	4.21 (3.47–5.11)	4.25 (3.5–5.17)	<0.0001
	41–42	152	3.44 (2.94–4.04)	3.31 (2.61–4.20)	3.30 (2.6–4.19)	<0.0001
	43–50	94	0.68 (0.55–0.83)	0.65 (0.50–0.85)	0.64 (0.49–0.84)	0.001
APL	Low density	449	3.49 (3.18–3.83)	Ref.	Ref.	
	Middle density	601	3.29 (3.03–3.56)	0.94 (0.83–1.06)	0.99 (0.87–1.11)	0.83
	High density	1511	3.53 (3.36–3.72)	1.01 (0.91–1.12)	1.15 (1.03–1.28)	0.01
Year	2010	267	3.07 (2.72–3.46)	Ref.	Ref.	
	2011	292	3.13 (2.79–3.51)	1.02 (0.86–1.20)	1.10 (0.93–1.29)	0.28
	2012	331	3.65 (3.28–4.06)	1.19 (1.01–1.40)	1.24 (1.06–1.46)	0.01
	2013	326	3.47 (3.12–3.87)	1.13 (0.96–1.33)	1.21 (1.03–1.43)	0.02
	2014	296	3.07 (2.74–3.44)	1.00 (0.85–1.18)	1.09 (0.92–1.28)	0.32
	2015	335	3.91 (3.52–4.36)	1.28 (1.09–1.50)	1.27 (1.08–1.49)	0.004
	2016	352	3.59 (3.24–3.99)	1.17 (1.00–1.37)	1.30 (1.1–1.52)	0.001
	2017	362	3.85 (3.47–4.27)	1.25 (1.07–1.47)	1.33 (1.13–1.56)	0.0004
FDEP	Advantaged	1245	3.52 (3.33–3.72)	1.05 (0.96–1.16)	1.05 (0.96–1.16)	0.31
	Intermediate	656	3.35 (3.10–3.61)	Ref.	Ref.	
	Disadvantaged	660	3.49 (3.23–3.77)	1.04 (0.94–1.16)	1.00 (0.9–1.12)	0.95

Note: Thirty-eight women who had used gonadotropin (1.5%) with a missing postcode were excluded. APL: tercile of the Local Potential Accessibility (Accessibilité Potentielle Localisée) to gynaecologist measures the spatial adequacy between supply and demand for care at the city level. FDEP: tercile of Social Deprivation Index (Indice de Désavantage Social) is an ecological measure that characterises the socio-economic environment in which individuals in a given geographic area live at a given time, based on the percentage of workers in the labour force, the percentage of high school graduates aged 15 and over, the percentage of unemployed in the labour force, and median household income.

[a]Adjusted rate ratio based on Poisson regression model including age group, Local Potential Accessibility to gynaecologists (APL), year, and Social Deprivation Index (FDEP).

[b]Ref. = reference category.

4 | DISCUSSION

This study, based on a large representative sample of the National Health Insurance Inter-Scheme Information System (SNIIRAM), showed significant variations in the drugs prescribed for infertility over the last 10 years. Although previous studies have already looked at the prescription of clomiphene citrate and its evolution over time, none has ever dealt with gonadotropins. We showed in this study that the prevalence rate and incidence rate of clomiphene citrate use significantly decreased between 2010 and 2017 by 20% (RR 0.80: 95% CI 0.71–0.90) and 23% (RR 0.77: 95% CI 0.66–0.89), respectively, while the prevalence rate and incidence rate of gonadotropin use increased by 11% (RR 1.11: 95% CI 1.01–1.22) and 33% (RR 1.33: 95% CI 1.14–1.55), respectively. Women's age and environmental factors (density of gynaecologists and social deprivation) affected these trends.

To our knowledge, no recent article has concomitantly examined the temporal trends in clomiphene citrate and gonadotropin use. One study, published in 2011, was carried out in the Netherlands on 1854 women aged 20–44, selected from a database of pharmaceutical prescriptions representative of the Dutch population.[9] The 2-year prevalence rate of clomiphene citrate use increased between 1998/99 (6.66 per 1000 women) and 2002/03 (7.24 per 1000 women), and decreased between 2004/05 (5.68 per 1000 women) and 2006/07 (4.82 per 1000 women). This result was partly explained by a decrease in the duration of clomiphene citrate use in women aged 30–39 who are increasingly using intrauterine insemination (IUI) or IVF, which requires the use of gonadotropins. Another study, published in 2012, evaluated the evolution of clomiphene citrate use over time in 26 993 women aged 20–49 from British Columbia (Canada) between 1997 and 2008, based on hospital and outpatient dispensations.[10] This study showed a decrease in the prevalence rate from 4.1 to 3.7 per 1000 women, while the incidence rate remained stable.

It is likely that the decrease in the prevalence rate of clomiphene citrate use observed in our study reflects a downward trend that began in the early 2000s, as reported in the above studies. The increase in the incidence rate of gonadotropins use is in line with what we anticipated given the social-demographic changes and the epidemiological context, however, the 8-year observation period is too short to allow us to attribute this finding to the increase in women's reproductive age alone. Indeed, this would have required a longer-term cohort. On the other hand, one cannot help thinking that the ageing of women of childbearing age in our cohort contributes in part to explaining this result. Two factors may be responsible for this: the change in the type of infertility and the increase in the number of cycles required to achieve a live birth. Indeed, as we have already mentioned, the type of infertility is different according to age with an increase in tubal infertility with ageing. The management of tubal infertility involves using ART and therefore gonadotropins.[14] It has also been shown that the probability of a live birth following IVF decreases with increasing female age, which may lead to an increase in the number of cycles and thus the use of gonadotropins.[15] In parallel with the ageing of women, the ageing of men at the time of conception also affects fertility, leading to an increase in the use of ART and therefore of gonadotropins.[16]

Although the incidence rate of clomiphene citrate use declined over time, age remained an important criterion for treatment initiation according to the multivariate analysis (ARR of 3.26 and 2.55 for the 25–30 and 31–35 age groups, respectively). This could be reassuring (for the quality of medical practices and patients) when we know that the causes of infertility are different according to age. Type II anovulation (normogonadotropic normoprolactinemic anovulation and polymicrocystic ovary syndrome) is an important cause of infertility in young women and clomiphene citrate is the treatment of choice in this case.[17,18] Indeed, in this indication the chances of obtaining a live birth with a first-line treatment of clomiphene citrate are about 40%.[19] Similarly, it is recommended that couples with unexplained infertility start with IUI + clomiphene citrate, do not use IUI + gonadotrophins, and use IVF in the event of failure.[20,21] Moreover, for women undergoing IUI after ovarian stimulation, for every birth gained with the use of gonadotropins—a treatment that is more expensive—there is a similar increase in the risk of multiple gestation.[21,22]

We also observed that the 25–30 age group was as strongly associated with the initiation of gonadotropin treatment as the 36–40 age group, even though the type of infertility most likely to occur in the former would require the use of clomiphene citrate in the first instance. This raises the question of whether clinicians are deviating from the recommendations of good practice.[23] It would be useful to identify the patients' care pathways and their determinants in order to analyse this phenomenon in more detail.

Clomiphene citrate initiation was higher when FDEP was higher (i.e., in disadvantaged areas). FDEP, it should be remembered, reflects the socio-economic status of an individual on the basis of the postal code of their residence. The higher it is, the lower their socio-economic status. This result has already been reported in the literature[10] and may be explained by the greater risk factors for infertility in this population (obesity, smoking, and alcohol).[24–27] Indeed, it is recognised that socio-economic status is associated with a risk of obesity, alcohol consumption, and tobacco use and that these factors, although debated for alcohol, are associated with a detrimental impact on fertility amongst women attempting to conceive. For example, a BMI ≥ 35.0 kg/m^2 compared to a BMI < 25 kg/m^2 was associated with a longer time to pregnancy in a population of 501 couples from Michigan and Texas without a diagnosis of infertility, and was observed for 12 months through a Cox model for discrete-time survival analysis.[24] At the same time, women with poor socio-economic status are usually younger at the time of their first pregnancy,[28] and such their infertility problem most often requires treatment with clomiphene citrate.[17,18] At first glance, the consequences may seem low given its low cost, around 3–7 euros per cycle, reimbursed at 65% by the health insurance, which is an out of pocket expense of 2–4.5 euros if the patient does not have complementary insurance. However, if the number of cycles is high and the patient is poor (without any complementary insurance), this can be a barrier to using the service.[29]

There was a positive association between a higher density of gynaecologists and higher treatment initiation for clomiphene citrate and gonadotropins. This association might be expected since it is known that physician density is associated with healthcare consumption, probably in relation to supplier-induced demand.[30,31] This association could also reflect a better access to gynaecologists in areas where their density meets the needs of the population.

It has been shown that if infertility care is not fully covered, a quarter of women who complete an IVF cycle stop treatment because they cannot afford the costs.[29] We might thus have expected an association between FDEP and gonadotropin use. In France, however, gonadotropins are almost always 100% covered and full coverage has been shown to reduce the number of people who do not seek care, which may explain the lack of association between FDEP and gonadotropin use in our study.[32]

One might ask what implications the results of this longitudinal study, which shows a decrease in the use of clomiphene citrate and an increase in the use of gonadotrophins in women treated for infertility, have for patients, clinicians and governments. If we are to have levers for action, we must identify the reasons for these trends. If the reasons are related to the aging of women of childbearing age, then we can only observe the facts. If deviations from good practice may be involved in these trends, then this needs to be demonstrated, particularly by looking at care pathways in more detail. As has already been widely discussed in the literature, variability in practice results in lower quality care, and higher health costs which are borne (in France) by the community.[33,34]

4.1 | Strengths and limitations

The first strength of this study is linked to the database used, which enabled us to access a representative sample of women who had undergone infertility treatment over a 7-year period. Our results can thus be extrapolated to the French population. Second, this database gave us an opportunity to describe the incidence rate accurately, since we were able to use a large exclusion period of 3 years. Third, because of the insurance coverage of infertility treatment, it is unlikely that we have missed women who have foregone care for financial reasons.[29] This study is thus, a priori, free of selection bias.

The weaknesses of this study are also related to the database. More nuanced trends could probably have been observed if we could have taken into account couple risk factors and infertility etiologies. But, these data were not available. However, this had no influence on the trends in drug prescriptions we found, which in itself remains a novel result. Finally, the FDEP is not an individual measure, but rather a municipality-wide measure in which there may be a disparity in socio-economic status that could lead to a classification bias. It is therefore possible that there were fewer poor women in the municipalities in which we found a higher clomiphene citrate initiation when FDEP was high, reducing our chance of concluding that there was a difference, which strengthens our results.

5 | CONCLUSION

Our results showed an increase in gonadotropin use for infertility treatment in France during the period 2010–2017 period, and a decrease in clomiphene citrate use, which was particularly observed in particular amongst the youngest women. In order to identify the factors associated with these changes, further work should be undertaken to analyse the use of these drugs in relation to women's care pathways.

FUNDING INFORMATION

This work was supported by the French Agence Nationale de la Recherche ANR StimHo project (grant ANR-17-CE36-0011-01).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ORCID

Bastien Bourrion https://orcid.org/0000-0002-5271-8677

REFERENCES

1. Sun H, Gong T-T, Jiang Y-T, Zhang S, Zhao Y-H, Wu Q-J. Global, regional, and national prevalence and disability-adjusted life-years for infertility in 195 countries and territories, 1990–2017: results from a global burden of disease study, 2017. *Aging*. 2019;11:10952-10991. doi:10.18632/aging.102497
2. European IVF-Monitoring Consortium (EIM) for the European Society of Human Reproduction and Embryology (ESHRE), Wyns C, De Geyter C, et al. ART in Europe, 2017: results generated from European registries by ESHRE. *Hum Reprod Open*. 2021;2021: hoab026. doi:10.1093/hropen/hoab026
3. Wesselink AK, Rothman KJ, Hatch EE, Mikkelsen EM, Sørensen HT, Wise LA. Age and fecundability in a North American preconception cohort study. *Am J Obstet Gynecol*. 2017;217(667):e1-667.e8. doi:10.1016/j.ajog.2017.09.002
4. Ben Messaoud K, Bouyer J, de La Rochebrochard E. Infertility treatment in France, 2008–2017: a challenge of growing treatment needs at older ages. *Am J Public Health*. 2020;110:1418-1420. doi:10.2105/AJPH.2020.305781
5. Huppelschoten AG, van Dongen AJCM, Verhaak CM, Smeenk JMJ, Kremer J a M, Nelen WLDM. Differences in quality of life and emotional status between infertile women and their partners. *Hum Reprod*. 2013;28:2168-2176. doi:10.1093/humrep/det239
6. Bahadur G, Homburg R, Bosmans JE, et al. Observational retrospective study of UK national success, risks and costs for 319,105 IVF/-ICSI and 30,669 IUI treatment cycles. *BMJ Open*. 2020;10:e034566. doi:10.1136/bmjopen-2019-034566
7. Bourrion B, Panjo H, Bithorel P-L, de La Rochebrochard E, François M, Pelletier-Fleury N. The economic burden of infertility treatment and distribution of expenditures overtime in France: a self-controlled pre-post study. *BMC Health Serv Res*. 2022;22:512. doi:10.1186/s12913-022-07725-9
8. Jacquesson L, Belaisch-Allart J, Ayel J-P. Induction of ovulation. *J Gynecol Obstet Biol Reprod*. 2010;39:S67-S74. doi:10.1016/S0368-2315(10)70032-6
9. Wang H, Land JA, Bos HJ, Bakker MK, de Jong-van den Berg LTW. Clomiphene citrate utilization in The Netherlands 1998-2007. *Hum Reprod*. 2011;26:1227-1231. doi:10.1093/humrep/der029
10. Lisonkova S, Joseph KS. Temporal trends in clomiphene citrate use: a population-based study. *Fertil Steril*. 2012;97:639-644. doi:10.1016/j.fertnstert.2011.12.034

11. Tuppin P, Rudant J, Constantinou P, et al. Value of a national administrative database to guide public decisions: From the système national d'information interrégimes de l'Assurance Maladie (SNIIRAM) to the système national des données de santé (SNDS) in France. *Rev Epidemiol Sante Publique*. 2017;65(Suppl 4):S149-S167. doi:10.1016/j.respe.2017.05.004
12. Rey G, Rican S, Jougla E. Measuring inequalities in mortality by cause of death. An ecological approach using an index of social disadvantage. *Bull Epidemiol Hebd*. 2011;8-9:87-90.
13. Barlet M, Coldefy M, Collin C, Lucas-Gabrielli V. Localized potential accessibility: a new measure of accessibility to private GPs. *Quest Déconomie Santé*. 2012;174:1-8.
14. Carson SA, Kallen AN. Diagnosis and management of infertility: a review. *JAMA*. 2021;326:65-76. doi:10.1001/jama.2021.4788
15. Recommendations | Fertility problems: assessment and treatment | Guidance | NICE. https://www.nice.org.uk/guidance/cg156/chapter/Recommendations
16. Paasch U, Grunewald S, Kratzsch J, Glander H-J. Obesity and age affect male fertility potential. *Fertil Steril*. 2010;94:2898-2901. doi:10.1016/j.fertnstert.2010.06.047
17. Practice Committee of the American Society for Reproductive Medicine. Use of clomiphene citrate in infertile women: a committee opinion. *Fertil Steril*. 2013;100:341-348. doi:10.1016/j.fertnstert.2013.05.033
18. Wang R, Kim BV, van Wely M, et al. Treatment strategies for women with WHO group II anovulation: systematic review and network meta-analysis. *BMJ*. 2017;356:j138. doi:10.1136/bmj.j138
19. Braam SC, de Bruin JP, Buisman ETIA, et al. Treatment strategies and cumulative live birth rates in WHO-II ovulation disorders. *Eur J Obstet Gynecol Reprod Biol*. 2018;225:84-89. doi:10.1016/j.ejogrb.2018.04.006
20. Penzias A, Bendikson K, Falcone T, et al. Evidence-based treatments for couples with unexplained infertility: a guideline. *Fertil Steril*. 2020;113:305-322. doi:10.1016/j.fertnstert.2019.10.014
21. Danhof NA, van Wely M, Repping S, et al. Gonadotrophins or clomiphene citrate in couples with unexplained infertility undergoing intrauterine insemination: a cost-effectiveness analysis. *Reprod Biomed Online*. 2020;40:99-104. doi:10.1016/j.rbmo.2019.09.004
22. Zolton JR, Lindner PG, Terry N, DeCherney AH, Hill MJ. Gonadotropins versus oral ovarian stimulation agents for unexplained infertility: a systematic review and meta-analysis. *Fertil Steril*. 2020;113:417-425.e1. doi:10.1016/j.fertnstert.2019.09.042
23. Cutler D, Skinner JS, Stern AD, Wennberg D. Physician beliefs and patient preferences: a new look at regional variation in health care spending. *Am Econ J: Econ Policy*. 2019;11:192-221. doi:10.1257/pol.20150421
24. Sundaram R, Mumford SL, Buck Louis GM. Couples' body composition and time-to-pregnancy. *Hum Reprod*. 2017;32:662-668. doi:10.1093/humrep/dex001
25. Hiscock R, Bauld L, Amos A, Fidler JA, Munafò M. Socioeconomic status and smoking: a review. *Ann N Y Acad Sci*. 2012;1248:107-123. doi:10.1111/j.1749-6632.2011.06202.x
26. Jones L, Bates G, McCoy E, Bellis MA. Relationship between alcohol-attributable disease and socioeconomic status, and the role of alcohol consumption in this relationship: a systematic review and meta-analysis. *BMC Public Health*. 2015;15:400. doi:10.1186/s12889-015-1720-7
27. Mínguez-Alarcón L, Chavarro JE, Gaskins AJ. Caffeine, alcohol, smoking, and reproductive outcomes among couples undergoing assisted reproductive technology treatments. *Fertil Steril*. 2018;110:587-592. doi:10.1016/j.fertnstert.2018.05.026
28. van Roode T, Sharples K, Dickson N, Paul C. Life-course relationship between socioeconomic circumstances and timing of first birth in a birth cohort. *PLoS One*. 2017;12:e0170170. doi:10.1371/journal.pone.0170170
29. Domar AD, Rooney K, Hacker MR, Sakkas D, Dodge LE. Burden of care is the primary reason why insured women terminate in vitro fertilization treatment. *Fertil Steril*. 2018;109:1121-1126. doi:10.1016/j.fertnstert.2018.02.130
30. Léonard C, Stordeur S, Roberfroid D. Association between physician density and health care consumption: a systematic review of the evidence. *Health Policy*. 2009;91:121-134. doi:10.1016/j.healthpol.2008.11.013
31. Delattre E, Dormont B. Fixed fees and physician-induced demand: a panel data study on French physicians. *Health Econ*. 2003;12:741-754. doi:10.1002/hec.823
32. ER1200.pdf. https://drees.solidarites-sante.gouv.fr/sites/default/files/2021-07/ER1200.pdf
33. Fisher ES, Wennberg DE, Stukel TA, Gottlieb DJ, Lucas FL, Pinder EL. The implications of regional variations in Medicare spending. Part 1: the content, quality, and accessibility of care. *Ann Intern Med*. 2003;138:273-287. doi:10.7326/0003-4819-138-4-200302180-00006
34. Fisher ES, Wennberg DE, Stukel TA, Gottlieb DJ, Lucas FL, Pinder EL. The implications of regional variations in Medicare spending. Part 2: health outcomes and satisfaction with care. *Ann Intern Med*. 2003;138:288-298. doi:10.7326/0003-4819-138-4-200302180-00007

SUPPORTING INFORMATION

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

How to cite this article: Bourrion B, Panjo H, François M, Pelletier-Fleury N. Trends in clomiphene citrate and gonadotropins use in women with infertility between 2010 and 2017: A population-based study in France. *Pharmacoepidemiol Drug Saf*. 2023;1-10. doi:10.1002/pds.5616