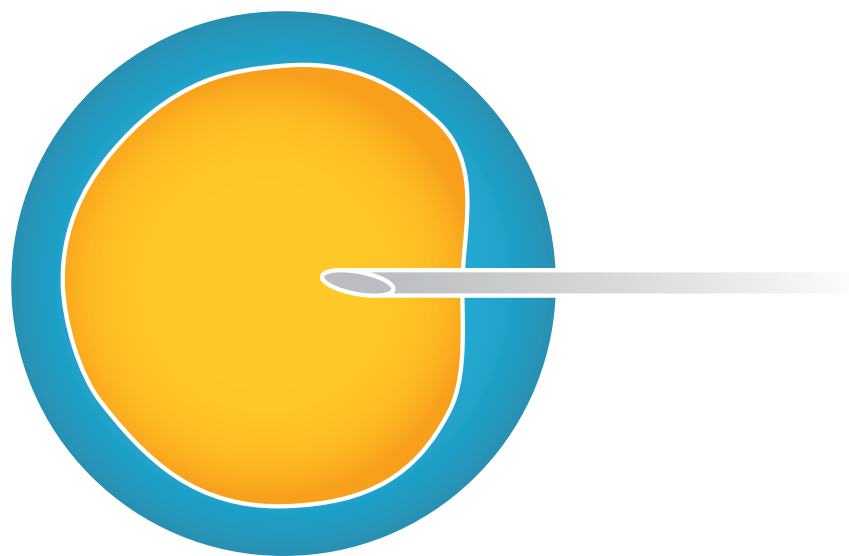


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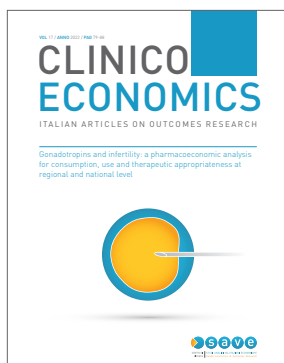
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Gonadotropins and infertility: a pharmacoeconomic analysis for consumption, use and therapeutic appropriateness at regional and national level



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# Gonadotropins and infertility: a pharmaco-economic analysis for consumption, use and therapeutic appropriateness at regional and national level

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## ABSTRACT EN

In vitro fertilization (IVF) has rapidly spread worldwide during the last four decades, these procedures are differently refunded by the public health systems of many countries in Western World. Hitherto there is the need to consider sustainability and to demonstrate a cost-beneficial profile.

In 2020, drugs for the genitourinary system and sex hormones represent the tenth category with the highest public expenditure, equal to 395.3 million euros and 1.7% of total public expenditure. The gonadotropin sub-category records the highest expenditure per capita. The active ingredient with the highest incidence of expenditure (23.6%) is represented by recombinant follitropin alfa.

The objective of this project consists in analyzing the national and regional market of gonadotropins and provide a pharmaco-economic evaluation of the drugs under analysis. The analysis of market data, related to health services contribution, combined with experimental evidences and epidemiological data are able to offer interesting insights on issues relating to economic sustain-

## ABSTRACT ITA

La fecondazione in vitro (FIV) si è rapidamente diffusa in tutto il mondo negli ultimi quattro decenni, con delle procedure che sono rimborsate in modo diverso dai sistemi sanitari pubblici di molti paesi del mondo occidentale. Pertanto vi è la necessità di considerare la sostenibilità e di dimostrare un profilo costi-benefici.

Nel 2020 i farmaci per il sistema genito-urinario e gli ormoni sessuali rappresentano la decima categoria con la spesa pubblica più alta, pari a 395,3 milioni di euro e l'1,7% della spesa pubblica totale. La sottocategoria delle gonadotropine registra la spesa pro capite più alta, il principio attivo con la maggiore incidenza di spesa (23,6%) è rappresentato dalla follitropina alfa ricombinante.

L'obiettivo di questo progetto consiste nell'analizzare il mercato nazionale e regionale delle gonadotropine e fornire una valutazione farmaco-economica dei farmaci in analisi. L'analisi dei dati di mercato, relativi al contributo dei servizi sanitari, unitamente alle evidenze sperimentali e ai dati epidemiologici sono in grado di offrire spunti interessanti su tematiche relative alla

ability and therapeutic appropriateness. In the analysis carried out, the sources considered take into account regional data in terms of IU (International Unit) and prices applied according with local tenders.

The analyses show the correspondence between virtuous regional instruments and the rationalization of spending.

We then simulated the effects on the market in terms of total annual cost when the drug was prescribed according to the benchmark of the virtuous regions. By adding together, the effects resulting from regional best practices in terms of therapeutic appropriateness and incentives for the use of biosimilars and/or low-cost drugs, an overall saving of € 3.458.837 could be achieved.

Therefore, in a universal health system, characterized by limited resources, it is of fundamental importance not to neglect these aspects of appropriateness and sustainability of long-term care and to evaluate the solutions available to generate greater homogeneity among the Regions and guarantee fairness of service on the territory according with the compliance to the indications for prescription and reimbursement.

sostenibilità economica e all'adeguatezza terapeutica. Nell'analisi svolta, le fonti considerate tengono conto dei dati regionali in termini di UI (Unità Internazionale) e dei prezzi applicati in base a gare locali.

Le analisi evidenziano la corrispondenza tra strumenti regionali virtuosi e razionalizzazione della spesa.

Abbiamo poi simulato gli effetti sul mercato in termini di costo annuo totale quando il farmaco è stato prescritto secondo il benchmark delle regioni virtuose. Sommando gli effetti derivanti dalle best practices regionali in termini di appropriatezza terapeutica e incentivi all'uso di biosimilari e/o farmaci a basso costo si potrebbe ottenere un risparmio complessivo di € 3.458.837.

Pertanto, in un sistema sanitario universale, caratterizzato da risorse limitate, è di fondamentale importanza non trascurare questi aspetti di adeguatezza e sostenibilità dell'assistenza a lungo termine e valutare le soluzioni disponibili per generare una maggiore omogeneità tra le Regioni e garantire l'equità del servizio sul territorio secondo il rispetto delle indicazioni per la prescrizione e il rimborso.

## INTRODUCTION

In vitro fertilization (IVF) has rapidly spread worldwide during the last four decades<sup>1</sup> procedure is refunded by the public health system in many countries in Western World.<sup>2,3</sup> As for all procedures being covered by public resources, there is the need to consider sustainability and to demonstrate a cost-beneficial profile.

Regardless of the need for sophisticated economic analyses, there is the undisputable dictat to scrutinize in-depth the IVF procedure in order to identify possible means to reduce costs and improve cost-effectiveness.

In 2020, drugs for the genitourinary system and sex hormones represented the tenth category with the highest public expenditure, equal to 395.3 million euros and 1.7% of total public expenditure. The gonadotropin sub-category recorded the highest expenditure per capita. The active ingredient with the highest incidence of expenditure (23.6%) was represented by recombinant follitropin alfa with a cost per day of therapy equal to 19.0 euros,<sup>4</sup> for the 75 IU (real units) formulation, which does not reflect the actual mean dosage used in the clinic, estimated at 150–225 IU.

In physiological terms, during antagonist cycles, if the dose is appropriate, it is presumed that follicular recruitment close to maximal from that latter stage of the luteo-follicular transition (4th day of FSH administration), could be sub-maximal because the circulating FSH concentration is lower for at least part of the 24-hour period.

Consequently, the use of modest daily doses of FSH (such as 150 IU) are recommended.<sup>5,6</sup> Many IVF programs aim to achieve high fresh pregnancy rates by targeting stimulation doses to obtain "ideal" egg yields – between 8 and 14 – which should also minimize the risk OHSS.

In addition, despite the absence of scientific evidence justifying doses of gonadotropins beyond 150–225 IU per day,<sup>7,8</sup> the use of higher dosages remains common, as reported by the data recorded in the national register of the PMA crossed with the international units detected by IQVIA.<sup>9</sup>

Therefore, among the recombinant follitropins, the first placed on the market, and most adopted, was the  $\alpha$ , for which two biosimilar versions are currently available. Subsequently, follitropin  $\beta$  and  $\delta$  were made available. Among the products of extractive origin are urofollitropin and menotropin. As regards luteinizing hormone, in addition to recombinant lutropin  $\alpha$ , a fixed combination with follitropin  $\alpha$  is also available. With regard to the treatment of female infertility, according to what is defined by the AIFA note 74, currently, gonadotropins are prescribed by the Italian NHS, based on the diagnosis and treatment plan of specialized structures, limited to women no older than 45 years with values of FSH, on day 3 of the cycle, not exceeding 30 mIU/ml.<sup>10</sup> The use of lutropin  $\alpha$ , in combination with a FSH-based preparation, is recommended for the stimulation of follicular development in the subgroup of adult women with severe insufficiency of LH and FSH.

The availability of different types of gonadotropins, recombinant or urinary/extractive, the introduction of biosimilar FSH, and the presence of a fixed combination of the recombinant modality with lutropin  $\alpha$  increase the choice of treatment. However, there is little information regarding the use of the different formulations in real regional clinical practice and what are the factors underlying the clinical choice of the type of gonadotropin. It is therefore interesting to photograph the national and regional market of gonadotropins, focusing attention on follitropin  $\alpha$ , for which, in addition to the originator product, its related biosimilar drugs and a fixed combination with lutropin  $\alpha$  are available.

In this study, we decided to focus on gonadotropin wastage, a neglected aspect that may harbor a relevant source of useless economic expenditure.<sup>11</sup> Duration of ovarian hyperstimulation cannot be predicted a priori and, therefore, one can inevitably expect some drug wastage.

The objective of this project was to analyze the national and regional market of gonadotropins and provide a pharmaco-economic evaluation of the drugs under analysis. The analysis of market data, combined with epi-

demiological data and consumption of health services, can offer interesting insights on issues relating to economic sustainability and therapeutic appropriateness.

## MATERIALS AND METHODS

Starting from the data coming from the database (DB) by IQVIA, which provided information on the use of gonadotropins, indicating the usage according to the stratified UI for the Italian regions. Analyses were carried out using Excel software with a time horizon ranging from January 2018 to December 2021 on the use of gonadotropins in Italy.

The drugs under analysis were the following: Meropur, Gonal F, Meriofert, Puregon, Bemfola, Ovaleap, Fostimon, Pergoveris, Luveris, Elonva, Rekovelle. In Table 1, we collected these drugs' consumption in Italy and the respective market shares in the different years considered. Then, we reported in Figure 1 the market shares trend for each drug over the time horizon.

As can be seen from the chart above, the COVID-19 pandemic and the consequent lockdown affected the general consumption of gonadotropins in 2020. Despite this, the 2021 data show a resumption of assisted reproduction cycles in Italian centers, as evidenced by the following histogram (Figure 2).

The analysis of the overall gonadotropin market also shows a sharp decline in consumption in 2020, with a partial recovery in 2021, randomly due to an increased transfer of previous cryo-preserved embryos and the diffusion of the freeze-all strategy.

Once the consumption in UI had been analyzed and calculated, we implemented the economic valorization of the single drugs starting from the prices charged by each contracting tender. In fact, it is known that the greatest bias is represented by the heterogeneity of the price of gonadotropins in the different regions (for convenience, the national average prices, as of December 2021, are shown in Table 2).

## RESULTS

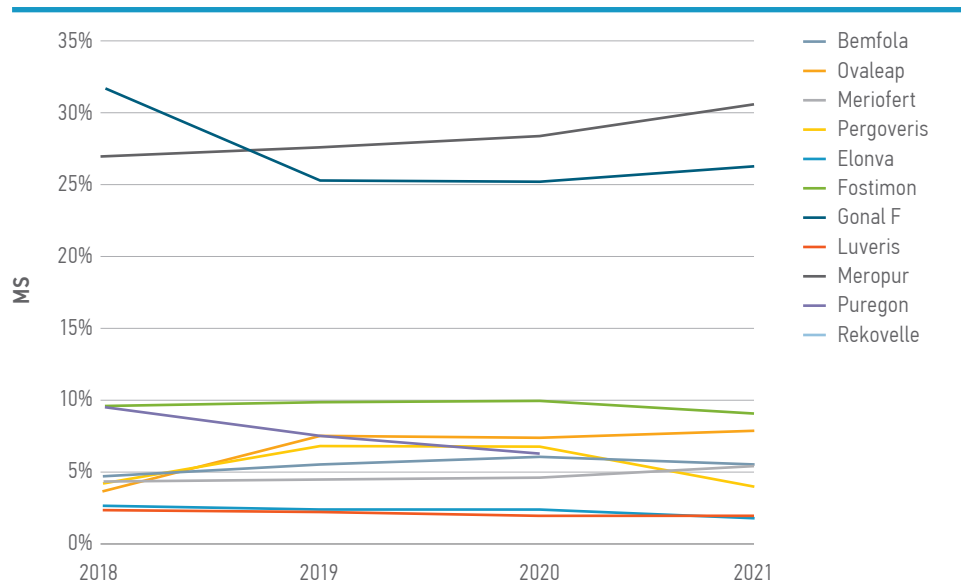
By crossing the above data (Table 1) with the tender prices (Table 2) and using the IU as weights, we were able to calculate the weighted average of the cost per IU in Italy (Table 3).

From the analysis of the data, extremely virtuous regions emerge, like Sicily, where the average price has significantly decreased. This was achieved thanks to the use of control tools (therapeutic plans) of prescriptive appropriateness that has generated a mechanism of increased competitiveness at the level of tenders.

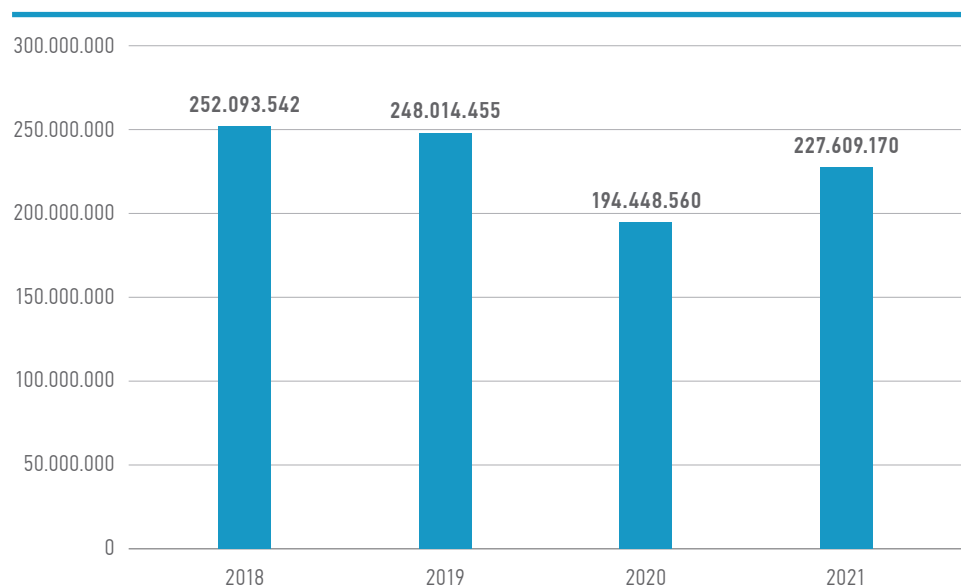
**TABLE 1**  
Gonadotropin consumption in Italy

Region	Product	2018		2019		2020		2021	
		Quantity	MS	Quantity	MS	Quantity	MS	Quantity	MS
Italy	Bemfola	111.663.700	5%	13.616.925	5%	11.840.100	6%	12.399.825	5%
Italy	Ovaleap	9.457.050	4%	18.526.500	7%	14.360.700	7%	18.018.000	8%
Italy	Meriofert	11.198.400	4%	11.022.225	4%	8.940.300	5%	12.287.325	5%
Italy	Pergoveris	10.387.050	4%	16.660.800	7%	13.249.050	7%	9.083.250	4%
Italy	Elonva	6.698.300	3%	5.846.050	2%	4.601.450	2%	4.201.400	2%
Italy	Fostimon	24.054.525	10%	24.421.275	10%	19.500.225	10%	20.821.425	9%
Italy	Gonal F	80.113.575	32%	62.898.375	25%	48.886.650	25%	59.767.425	26%
Italy	Luveris	5.984.475	2%	5.857.125	2%	3.721.500	2%	4.342.125	2%
Italy	Meropur	68.93.025	27%	68.377.950	28%	55.320.075	28%	69.815.775	31%
Italy	Puregon	24.419.700	10%	18.875.450	8%	12.184.950	6%	13.918.100	6%
Italy	Rekovelle	23.742	0%	1.911.780	1%	1.843.560	1%	2.954.520	1%
<b>Italy</b>	<b>Gonadotropins</b>	<b>252.093.542</b>	<b>100%</b>	<b>248.014.455</b>	<b>100%</b>	<b>194.448.560</b>	<b>100%</b>	<b>227.609.170</b>	<b>100%</b>

**FIGURE 1**  
Trends in gonadotropin consumption in Italy



**FIGURE 2**  
Total gonadotropin market in terms of IU in Italy



The regions that limited themselves to issuing guidelines of recommendations (e.g. Tuscany) did not achieve an appreciable result in terms of rationalisation of expenditure. Analyzing the data, we noticed that, on average, for each region, Pergoveris has a tendency to be overprescribed.

Through Excel, we then simulated the effects on the market in terms of total annual cost (and variation of

the same) when the drug was prescribed as in Sicily, considered a virtuous benchmark, with 0.24% against over 4.0% of the average Italian figure (YTD December 2021). Specifically, in the simulation, we have the possibility to absorb, through a slider, the difference (corresponding to 3.75%) between the market shares of Pergoveris in Italy with those in Sicily, by Bemfola, Ovaleap, Meriofert and Meropur.

Assuming a fair division of this difference between the four drugs (thus increasing the market share of each of them by about 1%), we observe a total saving in Italy of € 1.731.869. We then have the possibility, always through

the Excel tool, to select the single region in which we can observe the changes in the market resulting from this variation.

We also have the possibility of hypothesizing a reduction in the market shares of Gonal F in favor of biosimilars, Bemfola and Ovaleap, always using the criterion of equidistribution for the acquisition of market shares; this means that, having chosen the percentage of market share left to Gonal F compared to the initial one, through a cursor, we have distributed this share equally between the two biosimilar drugs.

In our simulation we assumed a 50% reduction in Gonal F market shares, which were distributed equally between Bemfola and Ovaleap. The total savings in Italy, *ceteris paribus* (without changing the shares of Pergoveris as mentioned above), amounted to € 1.726.968.

Adding the two effects mentioned, namely the redistribution of part of the Shares of Pergoveris equally

**TABLE 2**

Average tender costs per HPT product in Italy

Product	Italy
Bemfola	€ 0.192
Elonva	€ 0.220
Fostimon	€ 0.144
Gonal F	€ 0.240
Luveris	€ 0.343
Meriofert	€ 0.167
Meropur	€ 0.167
Ovaleap	€ 0.173
Pergoveris	€ 0.377
Puregon	€ 0.329
Rekoverle	€ 0.259

**TABLE 3**

Cost per IU in Italy- weighted average of all drugs

Region	2018	2019	2020	2021
Abruzzo	€ 0.22	€ 0.21	€ 0.22	€ 0.21
Basilicata	€ 0.25	€ 0.23	€ 0.21	€ 0.21
Calabria	€ 0.19	€ 0.19	€ 0.19	€ 0.18
Campania	€ 0.23	€ 0.23	€ 0.23	€ 0.21
Emilia Romagna	€ 0.23	€ 0.22	€ 0.21	€ 0.21
Friuli Venezia Giulia	€ 0.20	€ 0.22	€ 0.22	€ 0.20
Lazio	€ 0.20	€ 0.21	€ 0.21	€ 0.20
Liguria	€ 0.21	€ 0.22	€ 0.20	€ 0.20
Lombardia	€ 0.26	€ 0.26	€ 0.26	€ 0.26
Marche	€ 0.21	€ 0.21	€ 0.21	€ 0.20
Molise	€ 0.23	€ 0.21	€ 0.21	€ 0.19
Piemonte	€ 0.23	€ 0.24	€ 0.23	€ 0.20
Puglia	€ 0.24	€ 0.23	€ 0.21	€ 0.21
Sardegna	€ 0.19	€ 0.20	€ 0.20	€ 0.21
Sicilia	€ 0.18	€ 0.17	€ 0.17	€ 0.17
Toscana	€ 0.19	€ 0.20	€ 0.20	€ 0.19
Trentino Alto Adige	€ 0.21	€ 0.21	€ 0.21	€ 0.21
Umbria	€ 0.19	€ 0.20	€ 0.19	€ 0.19
Valle D'Aosta	€ 0.21	€ 0.25	€ 0.27	€ 0.21
Veneto	€ 0.20	€ 0.19	€ 0.19	€ 0.19
<b>Italia</b>	<b>€ 0.22</b>	<b>€ 0.22</b>	<b>€ 0.22</b>	<b>€ 0.21</b>



between Bemfola, Ovaleap, Meriofert and Meropur and the redistribution of part of the shares of Gonal F equally between Bemfola and Ovaleap, a total saving of € 3.458.837 is obtained.

These data are of particular interest in view of the specific indication of Pergoveris, whose use is recommended, and reimbursed in Italy, only in patients with severe LH and FSH deficiency, as per SmPC and document EPAR.<sup>12</sup> For this reason, Pergoveris has a higher price in comparison with all other gonadotropins (Table 2).

It is important to highlight that all other gonadotropins have broader therapeutic indications, not precluding use of these drugs also in patients with severe LH and FSH deficiency.

As reported in the aforementioned EPAR document,<sup>12</sup> this target population would consist of a small portion of patients that does not allow to provide a clinical explanation for the important consumption recorded in the analysis period.

The trend of use of the product is even less clear if we observe the regional cross-section with a considerable variability between the ratios and a probable inappropriate use in many patients. These considerations assume particular importance in light of the higher cost of follitropin  $\alpha$  and lutropin alfa therapy, leaving room for reflection on the appropriateness and sustainability of this treatment.

## DISCUSSION AND CONCLUSION

Sustainability topic allows us to deal with a further peculiarity of the follitropin  $\alpha$  market. Since 2015, the biosimilar version of the product is available, the use of which is capable of leading to a reduction in the cost of therapy, which, however, is still limited due to the low propensity to use the biosimilar compared to other therapeutic areas in which there is a greater penetration of this market (e.g. growth factors 97.2%). If at the Italian level in 2019 the market share for the originator drug was 66%, compared to 34% for biosimilars, at the regional level, once again, there is a considerable vari-

ability that leads the consumption of the originator to be above the Italian average in 10 regions. The substantial differences in the territory in terms of consumption of follitropin  $\alpha$  are clearly influenced by the presence of regional tenders for purchase. This does not apply to the combination of follitropin  $\alpha$ /lutropin  $\alpha$ , not participating in the tenders with follitropin  $\alpha$ , whose growing market penetration is justified, however, by the propensity of clinicians. Ultimately, the overuse of the originator and the increased use of follitropin  $\alpha$ /lutropin  $\alpha$  represent two dynamics that, in this market, limit the penetration of biosimilars and, as a consequence, the possible economic benefits obtainable for the Italian NHS.

The processed data are reliable in a very high percentage; within these, however, the level of reliability of the data for the Emilia-Romagna region is affected by the fact that the Region does not provide the total consumption data to IQVIA, imposing on the same a processing on data estimated in a higher percentage than the other Regions.

In a universal health system, characterized by limited resources, it is of fundamental importance not to neglect these aspects of appropriateness and sustainability of long-term care and to evaluate the solutions available to generate greater homogeneity among the Regions and guarantee fairness of service on the territory in compliance with the indications for prescription and reimbursement.

## DECLARATION OF COMPETING INTEREST

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

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