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Dosing Characteristics of Recombinant Human Luteinizing Hormone or Human Menopausal Gonadotrophin-Derived LH Activity in Patients Undergoing Ovarian Stimulation: A German Fertility Database Study

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Keywords
Ovarian stimulation · Luteinizing hormone · Real-world data · Human menopausal gonadotrophin · Recombinant human luteinizing hormone

Abstract
Objectives: The aim of the study was to evaluate dosing of recombinant human luteinizing hormone (r-hLH) or human menopausal gonadotrophin (hMG)-derived medications with LH activity in ovarian stimulation (OS) cycles for in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI). ***Design:*** A non-interventional study was performed to analyse data from the German RecDate database (January 2007–December 2011). ***Participants/Materials, Setting, Methods:*** Starting/total r-hLH/hMG dose, OS duration/cycle number, r-hLH/hMG initiation day (first day of administration), and population/cycle characteristics were assessed in women (≥18 years)

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undergoing OS for IVF/ICSI using r-hLH or hMG-derived medications (excluding corifollitropin alfa, clomiphene citrate, letrozole, mini/micro-dose human chorionic gonadotrophin, and urofollitropin alone). Data were summarized descriptively. ***Results:*** 67,858 identified cycles utilized medications containing r-hLH (10,749), hMG (56,432), or both (677). Mean (standard deviation) OS duration with r-hLH and hMG was 10.1 (4.43) and 9.8 (6.16) days, respectively. Median (25th–75th percentile) r-hLH starting dose (75.0 [75.0–150.0] IU) was consistent across patients regardless of age, infertility diagnosis, or gonadotrophin-releasing hormone (GnRH) protocol. Median (25th–75th percentile) hMG-derived LH activity starting dose was 225.0 (150.0–300.0) IU, regardless of GnRH protocol, but was lower in women aged <35 years and those with ovulation disorders/polycystic ovary syndrome. Median (25th–75th percentile) total dose for r-hLH (750.0 [337.5–1,125.0] IU) and hMG-derived LH activity (1,575.0 [750.0–2,625.0] IU) varied according to patients' age, infertility diagnosis, cycle number, and r-hLH/hMG initiation day. GnRH antagonist use resulted in a numerically higher median total hMG-derived LH activity dose than GnRH agonist use. ***Limitations:*** The data used in this study were taken from electronic medical records relating to a specific timeframe (2007–2011) and therefore may not accurately reflect current clinical practice; however, it is likely that the differences between the two compounds would be maintained. Additionally, secondary data sources may suffer from uniformity and quality issues. ***Conclusions:*** The standard of care for OS cycles is described with respect to IVF/ICSI treatment including an LH component in Germany during the specified timeframe.

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Introduction

Infertility is a disease of the female or male reproductive systems and is defined as the inability to achieve pregnancy after more than 12 months (or more than 6 months for women aged 35 years or older) of regular unprotected sexual intercourse [1, 2]. The estimated prevalence for infertility in Germany is 7.5% in women of childbearing age and 6.5% in men, based on a study that used data from the German Family Panel [3, 4]. According to the German In Vitro Fertilization (IVF) Registry (D·I·R) Annual Report 2019, the female indications for IVF include tubal pathology (22.5%), endometriosis (13.9%), ovulatory dysfunction (7.2%), hyperandrogenism/polycystic ovaries (4.8%), and psychogenic factors (0.3%), with the remainder due to "other factors" (including cervical factor) (24.0%), "no underlying pathology" (23.4%), or no information (0.4%). Each of these female indications may be accompanied by a male factor [5].

Natural female reproduction involves follicle development and ovulation coordinated by the complementary action of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) [6]. In the early follicular phase, in response to LH, theca cells convert cholesterol to androgens, which enter the granulosa layer and are converted to oestrogen via FSH-induced aromatization [7]. In granulosa cells, FSH- and LH-dependent actions activate intracellular signalling cascades that drive steroidogenesis, follicular maturation, ovulation, and luteinization [6, 8, 9]. The physiological function of LH and FSH is regulated by the hypothalamic-pituitary-gonadal axis, and impairment of this axis may affect gonadotrophin secretion and action, with subsequent loss of the intra-ovarian signalling cascades, ultimately leading to infertility [10].

Previously, only infertility caused by reduced circulating endogenous gonadotrophin levels (i.e., quantifiable LH and FSH production deficiency) was associated with conditions such as hypogonadotropic hypogonadism, and the spectrum of conditions was classified as WHO type 1 anovulatory disorders [11]. However, the definition of hypogonadotropic hypogonadism has since been expanded and now includes any gonadal failure (associated with reduced gametogenesis and reduced gonadal steroid production) due to reduced gonadotrophin production or action [12]. As such, LH and FSH deficiency is now recognized in a broader group of patients seeking fertility treatment [13–17]. In addition to disruption of the natural reproductive process, LH and FSH deficiency may be induced during ovarian stimulation (OS) treatment, i.e., through oral contraceptive pill pre-treatment or gonadotrophin-releasing hormone (GnRH) analogue co-treatment, resulting in a suboptimal response to OS [18, 19].

The classification of infertile patients based on ovarian response has led to individualized treatment in specific patient subpopulations [20]. During OS, protocols usually require exogenous gonadotrophins; and in many patients, OS with FSH alone is sufficient to induce multi-follicular development [21]. However, patients with LH and FSH deficiency undergoing OS also require exogenous LH, in addition to FSH, to maximize ovarian function [22, 23].

Recombinant human LH (r-hLH) is a highly pure source of LH and is co-administered with recombinant human FSH (r-hFSH) or administered as a fixed 2:1 ratio r-hFSH:r-hLH combination treatment. r-hLH was first approved by the European Medicines Agency in 2000 for

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the stimulation of follicular development in adult women [24]. Randomized controlled trials including women with severe LH and FSH deficiency showed that combination treatment with the fixed 2:1 r-hFSH:r-hLH combination treatment was safe and effective for inducing follicular development [25–28].

Menotrophins, including human menopausal gonadotrophin (hMG), have been marketed and used in reproductive medicine as an exogenous gonadotrophin to support follicular development for over three decades [29, 30]. Highly purified hMG (HP-hMG) products marketed in Germany are produced from the urine of post-menopausal women and contain equal amounts of urinary human FSH (u-hFSH) and LH activity, mainly driven via the action of human chorionic gonadotrophin (hCG), which is present in HP-hMG [30–33]. According to the indication, hMG is used as a standalone medication; nevertheless, in clinical practice, it is often used in combination with r-hFSH or u-hFSH [5].

Treatment protocols that include r-hLH and r-hFSH co-treatment and protocols that include hMG are commonly used to support follicular development [34, 35]. Individualization of OS based on patient characteristics, such as ovarian reserve and previous response to OS, results in varying gonadotrophin starting doses and intracycle dose adjustments, and it is not clear what doses of r-hLH or hMG-derived LH activity are being used during OS for IVF/intracytoplasmic sperm injection (ICSI) in routine clinical practice. Thus, the aim of this study was to describe the real-world dosing characteristics of r-hLH and hMG-derived LH activity, used as part of different protocols, in OS cycles for IVF/ICSI across fertility centres in Germany.

Materials and Methods

Study Design

This was a descriptive non-interventional cohort study based on secondary use of data collected from the RecDate database between 2007 and 2011. The RecDate database, programmed according to the software development environment FileMaker Pro, enabled the collection, documentation, and evaluation of reproductive medicine (ART cycles, daily injection doses, and follow-up data) from 71 fertility centres in Germany [36].

Patient Population

Women (aged ≥18 years) undergoing OS for IVF/ICSI treatment (first or subsequent cycle) with a protocol with either r-hLH- or hMG-containing medications using autologous oocytes (regardless of indication) were included. Treatment cycles with corifollitropin alfa, clomiphene citrate, letrozole, mini- or micro-dose hCG, or urofollitropin, if used alone (without LH) during the cycle, were excluded.

Study Medications

For the purposes of this publication and due to the differences in origin (recombinant or hMG-derived) of the LH activity, as well as to differences in possible treatment combination strategies, the study cohorts were defined as follows: (i) OS cycles for IVF/ICSI containing a medication with r-hLH (including ≥1 medication treatment line item of r-hLH and no medication containing hMG reported in the same treatment cycle); (ii) OS cycles for IVF/ICSI with a medication containing hMG-derived LH activity (including ≥1 medication treatment line item of hMG, and no medication containing r-hLH reported in the same treatment cycle); (iii) OS cycles for IVF/ICSI containing the use of both r-hLH and hMG. Medications containing only FSH (recombinant or urinary derived) were also assessed to define the possible gonadotrophin combination treatment strategies. Due to the possible cross-over in the combination strategies (e.g., treatment with hMG and r-hFSH in the same cycle), the dosing characteristics for medications containing FSH were not classified according to the origin (recombinant or urinary derived) and were generally described as FSH.

The r-hLH containing medications included in the database were Luveris® and Pergoveris®. The hMG medications included in the database were Merional® and Menogon HP®. The FSH medications included in the database were Bravelle®, Fostimon®, Gonal-f®, Puregon®, other u-hFSH, and other r-FSH.

If LH was received as part of a compound that contained both LH and FSH activity (e.g., 2:1 ratio r-hFSH:r-hLH combination treatment or a HP-hMG containing equal amounts of FSH and LH-like activity), the corresponding daily dose of exogenous LH and FSH received with different treatment strategies was calculated based on the LH and FSH ratio in that compound (e.g., 150 IU 2:1 ratio r-hFSH:r-hLH combination treatment equals 150 IU r-hFSH and 75 IU r-hLH and 225 IU HP-hMG equals 225 IU FSH and 225 IU LH activity). Total dose of LH was calculated as the sum of the daily doses (IU) of LH administered per cycle, and total dose of FSH was calculated as the sum of the daily doses (IU) of FSH administered per cycle.

Patient and Cycle Characteristics

The patient characteristics assessed at the start of a cycle were age (years), body mass index (BMI [kg/m^2]), and type of infertility (including endometriosis, ovulation disorders/polycystic ovary syndrome [PCOS], tubal factor, uterine/cervical factors, male factor, unexplained [idiopathic], other). The cycle characteristics assessed were type of treatment (conventional IVF, IVF/ICSI, other), GnRH protocol, medication used to trigger ovulation, type of combinations (treatment strategy), dose of LH and FSH (IU) at the start of each OS cycle (defined as starting dose), total dose of LH and FSH (IU) used for a complete cycle, the duration of OS (days), treatment rank (i.e., whether it was the first, second, third, fourth, or later treatment cycle), and day of LH stimulation initiation (cycles for which LH stimulation started at day 1 of OS and cycles for which LH stimulation started later).

Statistical Analysis

The scope of the study was to summarize data descriptively. No statistical comparisons between groups were performed, and any differences observed in the results between the groups are referred

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to as numerical rather than statistical differences. Categorical data were summarized by the number and percentage of patients in each category. Continuous data were summarized by the number of cycles, minimum and maximum values, mean, standard deviation (SD), median, and lower and upper quartiles. The analysis related to r-hLH/hMG dose was performed for the overall patient population, as well as the patient subgroups stratified according to age, GnRH protocol used, primary infertility cause, treatment cycle rank, and day of LH stimulation. No attempt has been made to remove or correct any unrealistic dose values assumed to be caused by data entry error.

Results

Patient Characteristics

A total of 67,858 OS treatment cycles for IVF/ICSI were identified: 10,749 cycles with a medication containing r-hLH, 56,432 cycles with a medication containing hMG, and 677 cycles in which both r-hLH and hMG products were used. Due to the comparatively low number in the third group (including the use of r-hLH and hMG products during the same treatment cycle), these cycles are not described further in this manuscript.

The mean (SD) age of the overall population was 36.2 (4.58) years, and mean (SD) BMI was 23.7 (4.51) kg/m^2. In total, 43,156 (63.6%) cycles were the first treatment cycle; 16,023 (23.6%) were the second; 5,716 (8.4%) were the third; and 2,963 (4.4%) were the fourth or later. Overall, 62.7% of cycles used a GnRH agonist protocol, and 18.1% of cycles used a GnRH antagonist protocol. Patients using GnRH antagonist were generally older (mean 37.1 [SD: 4.59] years) compared with patients using GnRH agonist (mean 35.8 [4.50] years). "Male factor" was the most frequent type of infertility (32.7%) overall, followed by tubal pathology (16.3%). Cycle characteristics were generally balanced across treatment groups (Table 1), except for recombinant hCG being used for ovulation triggering more often in cycles with r-hLH than with hMG (68.3% and 40.1%, respectively) and urinary hCG being used more often for ovulation triggering in cycles with hMG than with r-LH (59.5% and 29.9%, respectively). The mean (SD) duration of OS was 10.1 (4.43) days in the r-hLH group and 9.8 (6.16) days in the hMG group.

Treatment Strategies

A list of all treatment combinations assessed is shown in Online Resource 1. Three dominant combinations were observed among the treatment cycles with r-hLH medication: co-administration of r-hLH and FSH as two separate compounds (61.7%), 2:1 r-hFSH:r-hLH combination treatment (23.8%), and 2:1 r-hFSH:r-hLH combination treatment with an additional FSH compound (13.3%). In the hMG-derived LH activity group, only hMG (61.6%) and hMG with an additional FSH compound (38.4%) were observed.

Starting and Total Dose of LH and FSH

Some extreme (unrealistic) dose values were observed (such as very low or very high dose values, likely caused by data entry error); therefore, median values were used to describe dosing characteristics instead of mean, as median values are less sensitive to outliers. The median (25th–75th percentile) starting dose of r-hLH was 75.0 (75.0–150.0) IU, and the median starting dose of hMG-derived LH activity was 225.0 (150.0–300.0) IU, associated with a median starting FSH dose of 225.0 (150.0–300.0) IU in the r-hLH group and 225.0 (225.0–300.0) IU in the hMG-derived LH activity group (Fig. 1a). The median total r-hLH dose was 750.0 (337.5–1,125.0) IU, and the median total hMG-derived LH activity dose was 1,575.0 (750.0–2,625.0) IU, associated with a median total FSH dose of 2,006.0 (1,350.0–2,850.0) IU in the r-hLH group and 2,325.0 (1,500.0–3,300.0) IU in the hMG-derived LH activity group (Fig. 1b).

Dosing Characteristics According to Stratification Factors

Dosing characteristics of r-hLH, hMG-derived LH activity, and FSH according to the different stratification factors are demonstrated in Figures 2 and 3. The median starting dose of r-hLH was consistent across patient groups stratified by age (<35 years and ≥35 years), primary diagnosis for infertility, and the type of GnRH protocol (antagonist or agonist). The median starting dose of r-hLH increased from the third treatment cycle. The median starting dose of hMG-derived LH activity was not influenced by the type of GnRH analogue used but was lower in younger (<35 years) versus older (≥35 years) women, and in women with ovulation disorders/polycystic ovary syndrome versus other primary diagnoses of infertility. In both treatment groups, the median starting dose of LH differed in patients who started r-hLH or hMG on the first day of OS and in those who started r-hLH or hMG after the first day.

The median total dose varied across the patient groups stratified by the primary diagnosis of infertility, the number of treatment cycles, and according to age in both study groups (numerically higher doses seen in older patients). The median total dose of hMG-derived LH activity was also numerically higher in patients using GnRH antagonist versus GnRH agonist. Higher median total doses of both r-hLH and hMG-derived LH activity were seen in patients who started their r-hLH or hMG after the first day of OS compared with those who started on the first day of OS.

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Table 1. Cycle characteristics

	r-hLH (n = 10,749)	hMG-derived LH activity (n = 56,432)
Age, years		
n (%) with non-missing data	10,749 (100.0)	56,432 (100.0)
Mean (SD)	36.1 (4.27)	36.2 (4.64)
Median (25th, 75th percentile)	36.6 (33.2, 39.3)	36.8 (33.0, 39.6)
BMI, kg/m^2		
n (%) with non-missing data	10,489 (97.6)	55,380 (98.1)
Mean (SD)	23.2 (4.06)	23.8 (4.58)
Median (25th, 75th percentile)	22.3 (20.5, 24.9)	22.7 (20.8, 25.5)
Type of treatment, *n* (%)		
ICSI	7,916 (73.6)	38,960 (69.0)
IVF	2,274 (21.2)	13,733 (24.3)
IVF/ICSI	139 (1.3)	679 (1.2)
Not planned	420 (3.9)	3,060 (5.4)
Treatment cycle rank, *n* (%)		
First	6,777 (63.0)	36,054 (63.9)
Second	2,531 (23.5)	13,300 (23.6)
Third	970 (9.0)	4,650 (8.2)
Fourth or later	471 (4.4)	2,428 (4.3)
Type of infertility, *n* (%)		
Male factor	2,082 (30.7)	11,921 (33.1)
Tubal factor	909 (13.4)	6,056 (16.8)
Endometriosis	524 (7.7)	2,889 (8.0)
Ovulation disorders/PCOS	230 (3.4)	1,527 (4.2)
Uterine, cervical factor	79 (1.2)	354 (1.0)
Unexplained (idiopathic)	361 (5.3)	2,316 (6.4)
Other	2,592 (38.2)	10,991 (30.5)
Duration of OS, days		
n (%) with non-missing data	10,749 (100.0)	56,432 (100.0)
Mean (SD)	10.1 (4.43)	9.8 (6.16)
Median (25th, 75th percentile)	10.0 (8.0, 11.0)	10.0 (8.0, 11.0)
GnRH protocol used, *n* (%)		
Agonist	6,377 (59.4)	35,640 (63.3)
Antagonist	2,317 (21.6)	9,807 (17.4)
None	2,034 (19.0)	10,864 (19.3)
Medication used for ovulation triggering, *n* (%)		
GnRH agonist	181 (1.8)	169 (0.3)
r-hCG	7,024 (68.3)	21,404 (40.1)
u-hCG	3,071 (29.9)	31,755 (59.5)
Other	4 (0.0)	2 (0.0)

OS, ovarian stimulation; GnRH, gonadotrophin-releasing hormone; hMG, human menopausal gonadotrophin; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilisation; LH, luteinizing hormone; PCOS, polycystic ovary syndrome; r-hCG, recombinant human chorionic gonadotrophin; r-hLH, recombinant human LH; SD, standard deviation; u-hCG, urinary hCG.

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Discussion

This descriptive non-interventional real-world study, using data collected from routine clinical practice, assessed dosing characteristics of gonadotrophin compounds with exogenous r-hLH and hMG-derived LH activity in a population of patients undergoing OS for IVF/ICSI in Germany between 2007 and 2011. Dosing characteristics were assessed in the overall patient population as well as across subgroups of patients stratified by age, GnRH protocol, type of infertility, number of treatment cycles, and day of LH initiation. The study included data collected from 71 fertility centres in Germany, representing 55.5% of the centres in the country [37],

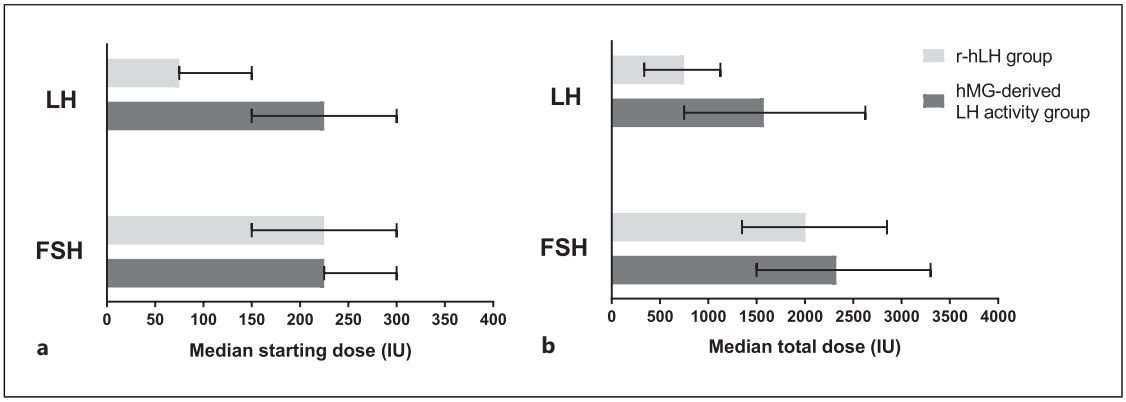

Fig. 1. Median starting (**a**) and total (**b**) dose of LH and FSH according to treatment group (r-hLH or hMG-derived LH activity).

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and therefore reflects the predominant treatment strategies used in clinical practice for OS during the specified timeframe.

The results showed that a larger proportion of OS cycles were initiated with hMG rather than r-hLH products during the study time period. The characteristics of women in both treatment groups were generally similar with regards to age, BMI, type of infertility, and number of previous treatment cycles, suggesting that the choice of urinary or recombinant LH products was not heavily influenced by patient characteristics. It has previously been reported that products containing LH are more likely to be used in patients with poor ovarian response, patients with advanced age, and those with previous unsuccessful IVF/ICSI treatment [11, 35, 38], suggesting that clinicians recognize specific subgroups of LH-deficient patients. A potential reason for the higher use of hMG observed in our study is that urinary-derived gonadotrophins have been used in reproductive medicine in Germany and other European countries for a longer period of time compared with recombinant gonadotrophins. Clinicians were likely more familiar with hMG products due to the longer history of clinical use compared with r-hLH products, such as Pergoveris, which received marketing approval in the European Union on June 25, 2007 [39].

In our study, the use of medications containing hMG was associated with numerically higher starting and total doses of LH and FSH compared with the use of r-hLH. The observed differences in dosing characteristics in our study are consistent with results of a worldwide survey assessing management of the sub-group of patients with poor ovarian response, which may require more individualized treatment approaches compared with the overall patient population included in our study [40]. The survey showed that 38% of physicians initiated treatment with the 75–150 IU starting dose of hMG and 25% initiated treatment with the ≥225 IU dose of hMG. Among physicians who prescribed r-hLH to their patients, 91% initiated treatment with the 75–150 IU dose of r-hLH and 9% with the ≥225 IU dose of r-hLH [40]. These findings suggest that the commonly prescribed starting dose of r-hLH in r-hFSH:r-hLH treatment of 75–150 IU is believed by clinicians to be sufficient to support follicular development. Furthermore, a previous study using data from the German RecDate system database [41] showed that the total dose of r-hFSH was significantly lower in patients treated with a 2:1 fixed combination of r-hFSH:r-hLH compared with hMG alone or compared with combination treatment of hMG and r-hFSH ($p < 0.001$). As LH was received in a fixed ratio with FSH in both cases, patients receiving r-hFSH:r-hLH were also exposed to a lower dose of LH compared with the dose of hMG-derived LH-like activity in those receiving hMG, consistent with the observations from our study [41].

In our analysis, we show that the main factors associated with dosing of r-hLH and hMG-derived LH activity were age, primary diagnoses of infertility, number of treatment cycles, and day of LH or hMG initiation. The starting and total dose of hMG-derived LH activity were generally lower in younger (<35 years) versus older patients (≥35 years), and in women with ovulation disorders/PCOS versus women with other primary diagnoses of infertility. The starting dose of r-hLH did not differ according to age or primary diagnosis of infertility; however, the total dose was also generally higher in older patients. In the r-hLH group, both the starting and total dose increased with the number of stimulation cycles. In

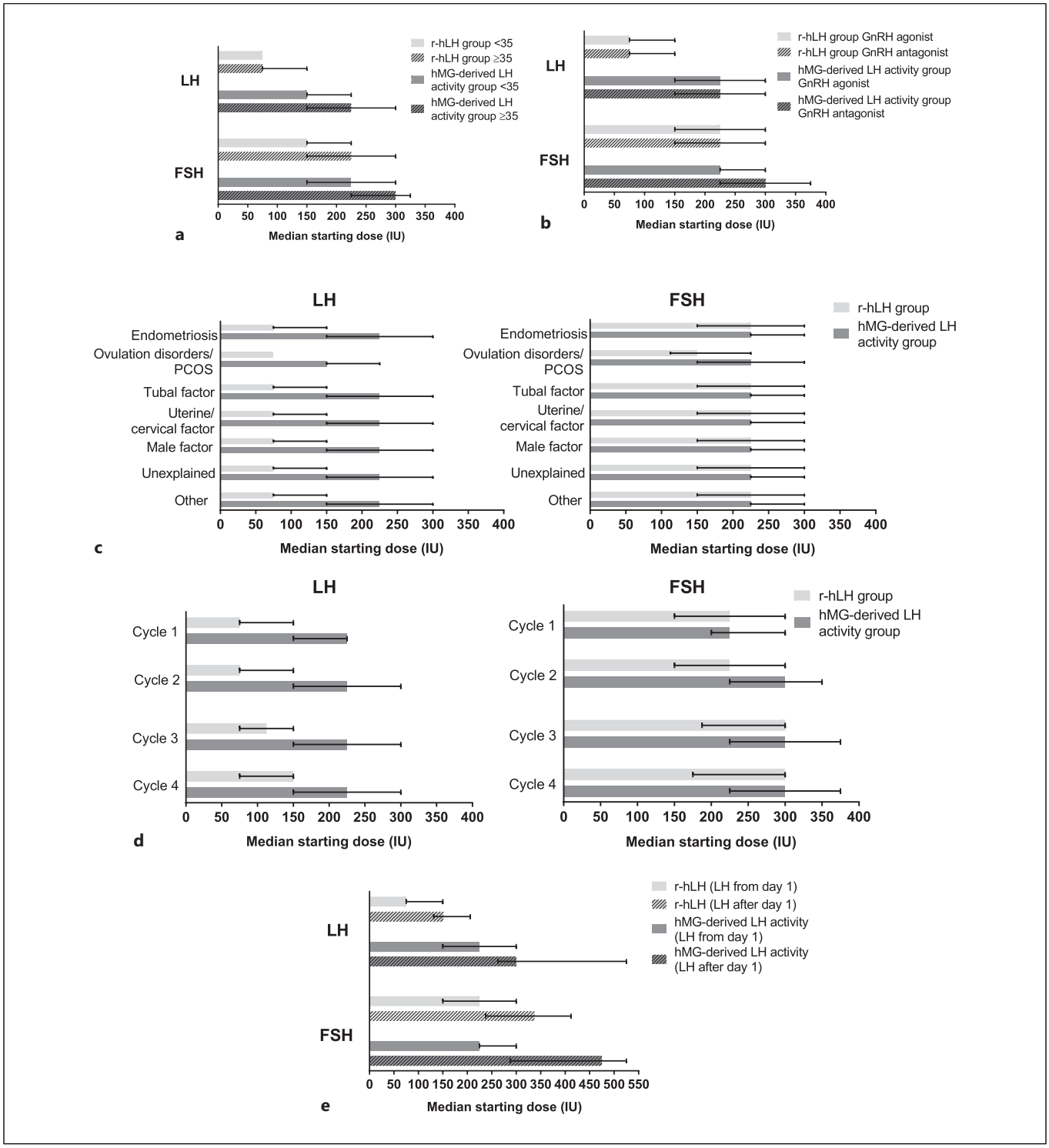

Fig. 2. Median starting doses of LH and FSH according to treatment group (r-hLH or hMG-derived LH activity) and age (<35 or ≥35 years) (**a**), type of GnRH protocol (agonist vs. antagonist) (**b**), type of infertility (**c**), treatment cycle rank (**d**), and day of LH initiation (**e**).

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the hMG group, only the total dose increased with the number of stimulation cycles, commencing with the third cycle. These observations confirm that clinical practice is in favour of individualization of the starting dose for each initiated cycle and intra-cycle dose adjustments. In general, it is recognized that the response to OS varies in different patient subgroups and that a "one-size fits all" approach for OS is no longer acceptable in reproductive medicine [20]. For example, although a previous study found no improvement in live birth rate with antral follicle count (AFC)-based individualized FSH dosing compared with standard FSH dosing for the population as a whole, they concluded that individualized dosing may benefit specific populations, such as hyper-responders [42]. However, it should be noted that dose adjustments were not allowed during OS but only allowed between cycles, which may have increased the proportion of high response in the 150 IU starting dose group and the proportion with suboptimal response in the 100 IU group [43]. It is also important to note that dose individualization at the start of the treatment and intra-cycle dose adjustments are common in clinical practice [44, 45].

We observed higher doses of hMG in the GnRH antagonist cycles versus agonist cycles. This is in contrast with the well-recognized concept that antagonists reduce the total dose of gonadotrophins [46]. However, this could be explained by the older age of patients using GnRH antagonist (vs. agonist) in our study. We also observed that patients who started r-hLH or hMG after the first day of OS had a higher starting and total dose of both r-hLH and hMG-derived LH activity versus those who started r-hLH or hMG on the first day of OS. This is often seen in clinical practice and is not surprising given that r-hLH or hMG added later in a cycle is usually started at a higher dose (in order to compensate for the insufficient follicular development during the first few days of the treatment) and that the overall stimulation cycle is usually longer, resulting in more product being used in total [41].

Generally, in the population analysed here, we observed that the starting and cumulative doses of hMG-derived LH activity were higher than the doses of r-hLH. This suggests that a higher dose of hMG-derived LH activity is required to achieve a similar clinical effect during OS to that seen with r-hLH. LH activity for both hMG-derived and r-hLH had been considered equivalent until recently. This consensus originated from past in vivo and in vitro experimental models using rodents or rodent-derived cells; however, because rodents do not express chorionic gonadotrophin subunit beta 3, they do not produce CG. Furthermore, the rodent LH receptor is not identical to the human receptor, so any conclusions made on rodent models have been recently revised based on human in vivo and in vitro experimental models. In humans, the different molecular features of LH and hCG lead to hormone-specific LHCG receptor binding and intracellular signalling cascades. LH preferentially activates phospho-extracellular-regulated kinase 1/2 (ERK1/2) and AKT (also known as protein kinase B) pathways, leading to proliferative and anti-apoptotic signalling and partial agonism of progesterone production [6], whereas hCG activates cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA)-mediated steroidogenic and pro-apoptotic pathways [6]. These recent findings contradict the general consensus that LH and hCG are equivalent since they bind to the same receptor. Finally, it is worth noting that the in vivo rat assay [47] is still being used to calibrate urine-derived gonadotrophin preparations used in medical practice. Recombinant human gonadotrophins are filled by mass with a clearly lower batch-to-batch variability. This potentially explains the different doses of LH and hMG-derived LH activity used in clinical practice [6] and observed in this study.

A strength of our study is the large number of patients included across multiple fertility centres, thereby reflecting the common treatment strategies regarding recombinant and urinary gonadotrophin use during the specified time period. However, as with many healthcare secondary data sources, the data available in electronic medical records often have limitations regarding uniformity and quality, with incomplete records commonly reported. The assessment of exposure to each medication in this study could only be based on the existing data and depended on how accurately physicians recorded the different variables. For example, poor ovarian response may affect starting dose and total dose exposure but is often not well recorded in patient charts and then not well captured in electronic medical records extracted from these patient charts. Another example is the observed extreme dose values, some of which may be unrealistic and may rather be linked to mistakes in data entry. We chose to include the extreme values in this analysis but used the median instead of the mean to describe dosing characteristics, as the median values are less sensitive to the outliers. In addition, no prespecified thresholds for extreme dose values were defined during the study.

This study has other limitations. As the data relate to a specific timeframe that was a number of years ago (2007–2011), practices will likely have changed since

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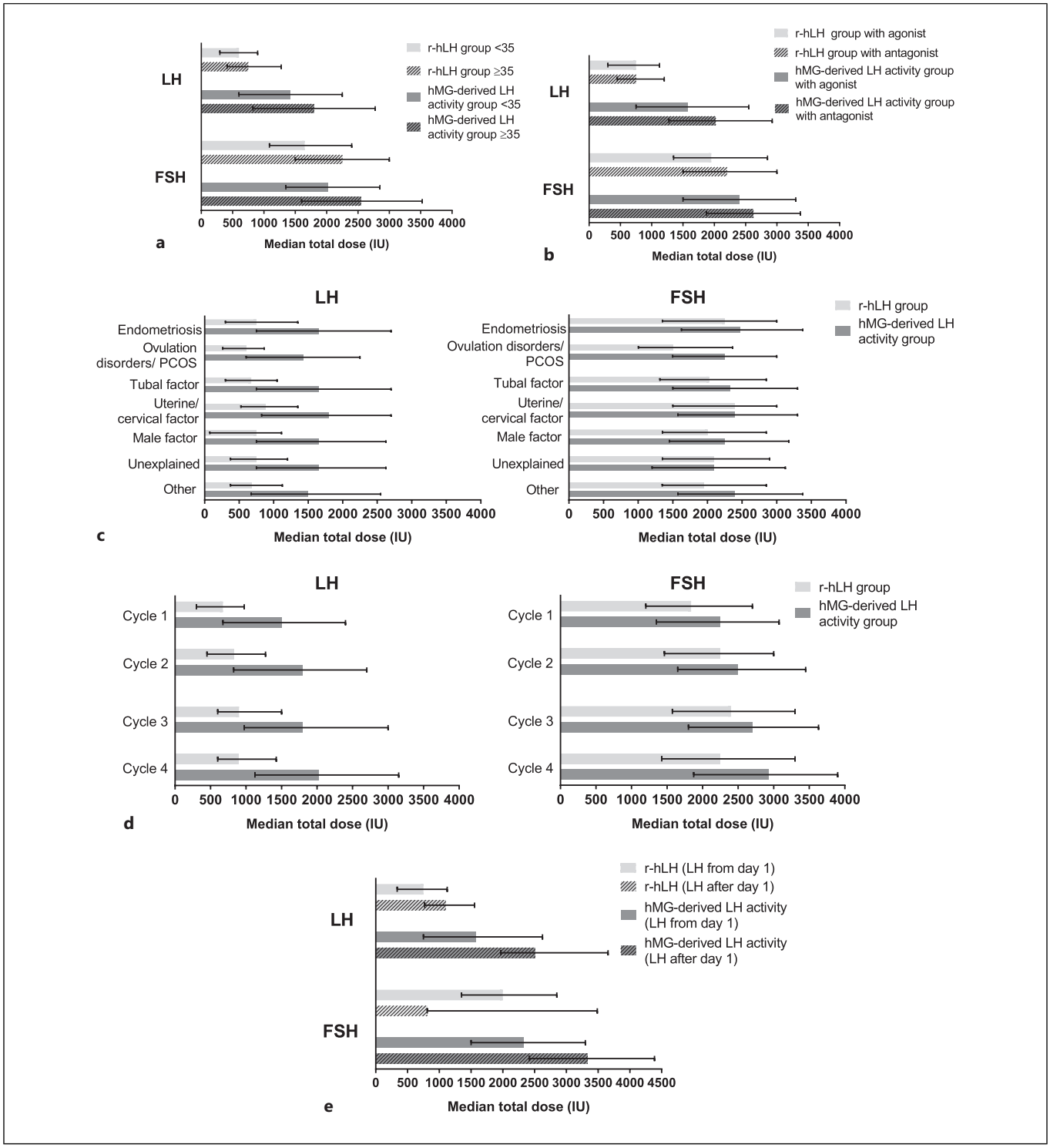

Fig. 3. Median total doses of LH and FSH according to treatment group (r-hLH or hMG-derived LH activity) and age (<35 or ≥35 years) (**a**), type of GnRH protocol (agonist vs. antagonist) (**b**), type of infertility (**c**), treatment cycle rank (**d**), and day of LH initiation (**e**).

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this time, and validating these data using a more recent database with comparable analyses would be valuable. However, any potential changes to GnRH downregulation protocols and agents used for OS can reasonably be expected to impact both hMG and r-hLH/r-hFSH equally, and we hypothesize that the differences observed between the two compounds would likely be maintained if more recent real-world data were considered. A medication containing the 2:1 ratio of r-hLH:r-hFSH was launched in Germany on October 15, 2007 [48], but the collection of data regarding this medication in the RecDate database did not start until January 1, 2008. As this was a non-interventional cohort study based on the secondary use of data collected from the RecDate database, the outcomes assessed were not corrected for age and other baseline and treatment characteristics; therefore, differences in dosing characteristics might be related to the differences between patient groups, and no clinical outcomes were compared in our analysis. However, in a previous meta-analysis assessing the use of FSH and LH, a significantly higher pregnancy rate was reported for the cycles with r-hLH and FSH versus cycles with hCG and FSH in 989 patients, representing five of the 70 studies included in the meta-analysis [49]. Several other studies have shown the benefit of r-hFSH:r-hLH (2:1) fixed combination treatment compared with hMG in terms of implantation rate, number of cycles required to achieve pregnancy, clinical pregnancy rate, and live birth rate [41, 50–53]. Further analysis of the real-world data collected via RecDate could be conducted to compare clinical outcomes and cost-effectiveness between urinary-derived and recombinant LH gonadotrophins.

Conclusion

This descriptive non-interventional cohort study of OS cycles for IVF/ICSI across fertility centres in Germany shows that the median (25th–75th percentile) r-hLH starting dose of 75 (75–150) IU is used across populations stratified by age (<35 vs. ≥35 years), primary infertility diagnosis, and the type of GnRH protocol (antagonist or agonist). The median (25th–75th percentile) starting dose of 225 (150–300) IU of hMG-derived LH activity was not influenced by the type of GnRH but was lower (150 IU) in women aged <35 years compared with women aged ≥35 years, and in women with ovulation disorders/PCOS as the primary diagnosis compared with women with other primary diagnoses of infertility. Future studies should be conducted to compare the effectiveness of equivalent doses (75 IU vs. 75 IU and 150 IU vs. 150 IU) of r-hLH versus hMG-derived LH activity in terms of clinical outcomes.

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Statement of Ethics

No ethics review board approval was required as this study was based on secondary use of data from the German in vitro fertilization registry (RecDate), which is an established system used in reproductive centres by the Deutsches IVF-Register (D·I·R) to record and store anonymised data for quality assurance purposes. Written informed consent from participants was not required in accordance with local/national guidelines.

Conflict of Interest Statement

Julie Hubbard and Joan Schertz are employees of EMD Serono Research and Development Institute, Inc., an affiliate of Merck KGaA, Darmstadt, Germany. Salvatore Longobardi and Monica Lispi are employees of Merck Healthcare KGaA, Darmstadt, Germany. Klaus Bühler has received honoraria from Merck KGaA, Darmstadt, Germany; Bayer; Takeda; Ferring; and Stiftung Endometrioseforschung; and is the recipient of a grant from Theramex. Valerie Strezsak and Patrice Verpillat were employees of Merck Healthcare KGaA, and Arthur Allignol was an employee of EMD Serono Research and Development Institute Inc., at the time of the study.

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Author Contributions

Valerie Strezsak, Arthur Allignol, Julie Hubbard, Joan Schertz, and Patrice Verpillat contributed to the conception and the design of the study. Valerie Strezsak, Arthur Allignol, Klaus Bühler, Robert Fischer, Julie Hubbard, Salvatore Longobardi, Monica Lispi, Joan Schertz, and Patrice Verpillat contributed to the interpretation of the data, review and critical revision, and approval of the manuscript.

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Data Availability Statement

Any requests for data by qualified scientific and medical researchers for legitimate research purposes will be subject to Merck KGaA's Data Sharing Policy. All requests should be submitted in writing to Merck KGaA's data sharing portal https://www.merckgroup.com/en/research/our-approach-to-research-and-development/healthcare/clinical-trials/commitment-responsible-data-sharing.html. Enquiries can also be directed to the corresponding author. When Merck KGaA has a co-research, co-development, co-marketing, or co-promotion agreement, or when the product has been out-licensed, the responsibility for disclosure might be dependent on the agreement between parties. Under these circumstances, Merck KGaA will endeavour to gain agreement to share data in response to requests.

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