A Review on the Economic Evaluation of Infertility Pharmacologic Agents in North America and European Countries

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Background

- Failure to achieve pregnancy after 12 months of regular unprotected intercourse with the same partner in women below 35 years old (6 months in women 35 years and older) is defined as infertility. Globally, 48 million couples and 186 million individuals face challenges with fertility.
- Infertility has been underdiagnosed and undertreated for cultural reasons for several years. Even though multiple pharmacologic and non-pharmacologic interventions are currently available, in many countries, accessibility, availability, and quality of these interventions remain challenging. The access problem stems from lack of necessary infrastructure, trained clinicians, strong effectiveness data, and high costs of intervention, even in countries that are vigorously sea eking information on the latest infertility treatments. Many countries require not only effectiveness, but robust cost-effectiveness data to decide on types of interventions that should be prioritized for infertility treatment.
- This literature review will benchmark the design and outcomes of CE studies for fertility agents to help better inform decision-makers on the available data and perspectives in this important therapeutic area.

Objective

Primary Objective

- To assess the current scope of cost-effectiveness of fertility agents in North America and European countries

Secondary Objectives

- To categorize common inputs, outcome measures, and major findings of these evaluations
- To describe the similarity of conclusions and recommendations of included analyses

Methods

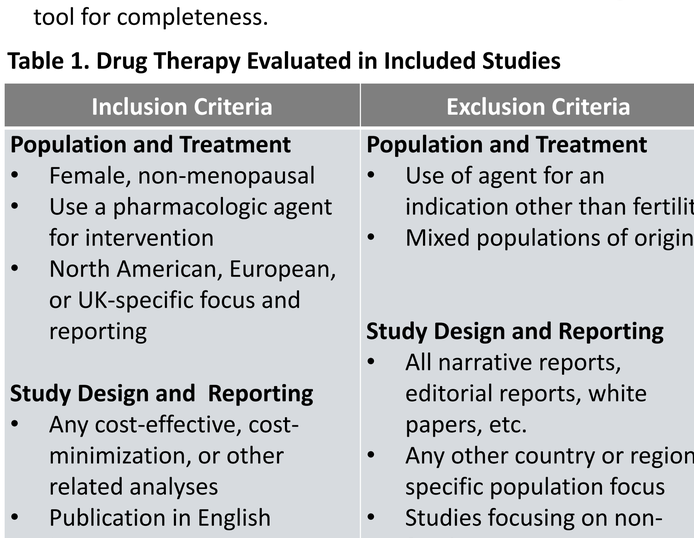
- A multimodal approach was used to conduct this comprehensive review of the published literature including systematic search and collection as well as the hand search method. Literature searches took place in Medline OVID and Web of Science. Hand pull collection was conducted from ASRM and ACOG. Search limitations were imposed to capture time-relevant publications from 2001 to 2022.
- Studies were assessed in the screening phase against strict inclusion and exclusion criteria found below in *Table 1*. All studies identified were indexed in a reference management tool for completeness.

Table 1. Drug Therapy Evaluated in Included Studies

Inclusion Criteria	Exclusion Criteria
Population and Treatment • Female, non-menopausal • Use a pharmacologic agent for intervention • North American, European, or UK-specific focus and reporting **Study Design and Reporting** • Any cost-effective, cost-minimization, or other related analyses • Publication in English language	**Population and Treatment** • Use of agent for an indication other than fertility • Mixed populations of origin **Study Design and Reporting** • All narrative reports, editorial reports, white papers, etc. • Any other country or region-specific population focus • Studies focusing on non-fertility

The PRSMA diagram below summarizes the initial identification, screening, and extraction phase outputs. Total of 3159 records were identified in Medline OVID, Web of Science, ASRM and ACOG conferences, of which 2507 were removed due to duplications, language and specified study timeframe. Of the screened records, 32 total records were included in this study.

Figure 1. PRISMA diagram



Results

Of the 32 studies included in the TLR, 81.3% were cost-effectiveness analyses, 12.5% were total cost-of-care comparisons, 3.1% were cost-minimization analyses, and 3.1% were discrete choice experiments/simulation evaluations. Of the 17 studies with designated perspectives, 7 (41.2%) were from a healthcare/system perspective, 6 (35.3%) were that of a payer, and 4 (23.5%) were societal. Study characteristics of these analyses by country are presented in *Table 2* below.

Of the included studies and evaluations, half were published between 2002 to 2012, and the remaining half were reported since 2013. More than half of the studies (53.1%) were reported in Euros, the remainder in USD (28.1%) or pounds (18.8%). Of the 32 studies, 21 (65%) reported cost ratios (*Table 2*).

Table 2. Study characteristics based on the countries of origin[a]

Countries	# of Studies	Cost-Year		Outcome Measures		Data Inputs
		2001-13	2014-22	ICER	NB[b]	RCT
EU-5	11 (34%)	8 (73%)	2 (18%)	6 (55%)	5 (45%)	8 (73%)
NL	10 (31%)	5 (50%)	5 (50%)	6 (60%)	4 (40%)	6 (60%)
US	6 (19%)	3 (50%)	3 (50%)	2 (33%)	4 (67%)	0 (0.0%)
BE, HU, SE[c]	6 (19%)	5 (83%)	1(17%)	2 (33%)	4 (67%)	2 (33%)
Total	33	21	11	16	17	16

[a]One study's population spanned between the UK and NL [b]NB reports both overall savings and net benefits calculations. [b]BE: Belgium, HU: Republic of Hungary, SE: Sweden

Figure 2 describes therapies evaluated in included studies either in different regimens (length and drug combination variable) and dose intensities. Screening, miscarriage-prevention, and preterm birth prevention pharmaceutical agents are classified as pre/post agents. Patients used within cycles to achieve pregnancy are classified as within-cycle agents.

Figure 2. Drug Therapy Evaluated in Included Studies

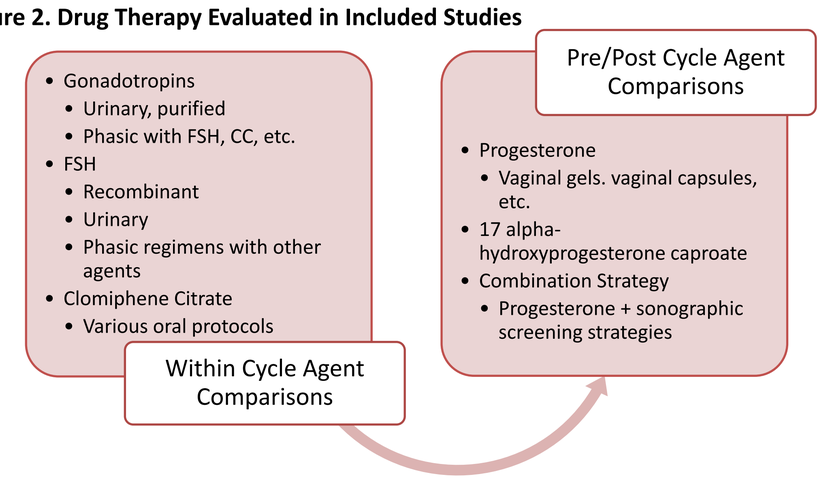


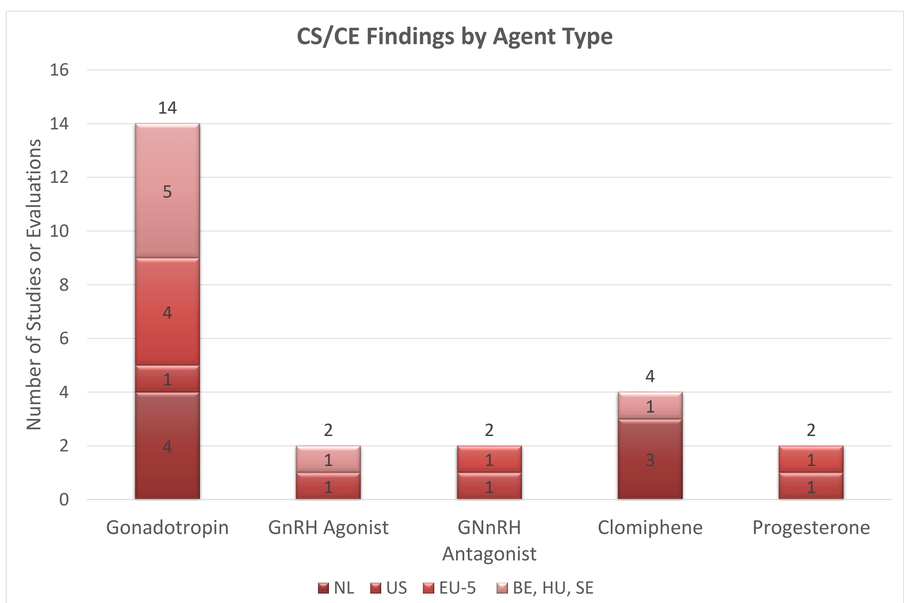
Table 3 represents the number of studies identified with major drug-related findings categorized by country. Overall, 14 (44%) of the studies reported at least one major finding regarding the use of gonadotropins including FSH and LH products.

Table 3. Major Drug-related Cost- Saving or Cost-Effective findings by country[a,b]

	Total[c] (n= 32)	NL[c] (n=10)	US (n= 6)	EU-5[c] (n=11)	BE, HU, SE (n=6)
Gonadotropin	14	4	1	4	5
GnRH Agonist	2	0	1	0	1
GNnRH Antagonist	2	0	1	1	0
Clomiphene	4	3	0	0	1
Progesterone	2	0	1	1	0

[a]Studies were included in the count if ≥1 findings indicated cost savings or cost-effectiveness, [b] CS: Cost-Saving, CE: Cost-effective, [c]One study's population spanned between the UK and NL

Figure 3. Major Drug-related Cost- Saving or Cost-Effective Findings by Agent Type[a,b]



[a]CS: Cost-Saving, CE: Cost-effective, [b]BE: Belgium, HU: Republic of Hungary, SE: Sweden

Results *(continued)*

Figure 3 shows the major cost-related findings in each class of infertility medication. GnRH-agonist, GnRH-antagonists, and progesterone products are the least frequently reported with major cost-related findings (2 studies for each).

Table 4. Focus of Major CS/CE Recommendations Reported[a,]

	Total[b] (n= 32)		NL[c] (n=10)		US (n= 6)		EU-5[c] (n=11)		BE, HU, SE (n=6)	
	CS/CE	Policy	CS/CE	Policy	CS/CE	Policy	CS/CE	Policy	CS/CE	Policy
Gonadotropin	10	1	2	0	0	0	4	1	3	0
GnRH agonist	1	0	0	0	0	0	0	0	1	0
GNnRH Antagonist	1	0	0	0	0	0	1	0	0	0
Clomiphene	2	0	1	1	0	0	0	0	0	0
Progesterone	2	0	0	0	1	0	1	0	0	0

[a]Studies were included in the count if ≥1 finding indicated cost savings or cost-effectiveness, [b] CS: Cost-Saving, CE: Cost-effective, [c]One study's population spanned between the UK and NL

Table 4 describes the number of studies identified with major recommendations. The recommendations are categorized into cost-related versus policy-related. While 50% of the studies reported at least one cost-related recommendation, only one study was identified with a policy-related recommendation.

Some evaluations noted that they were limited in drawing conclusions and providing recommendations on cost savings or effectiveness due to lack of standard costs, variability of reimbursement, and variability in treatment decisions and practices. Studies tended to report that willingness to pay (WTP) would largely impact the decision of infertility regimen depending on the country.

Limitations

- Variability was observed between study designs, limiting the opportunity to conduct direct comparisons.
- Half of the included studies were conducted between 2001-2010 so they could not capture the most recent treatment protocols and new supportive technologies.
- Many within-drug and between-drug comparisons were conducted, limiting the ability for standard comparisons between drug types.
- Different countries use various variables, metrics, and thresholds to capture efficacy, cost, and cost-effectiveness, liming generalizability.
- Many fertility-focused economic analyses look to evaluate cycle regimens, lacking focus on specific pharmaceutical agents, therefore limiting relevancy to this specific investigation's aim.

Conclusions

- Most evaluations focused on gonadotropins as a drug class and provided recommendations on cost savings or effectiveness with an apparent limitation of generalizability.
- As most models were from the payor or healthcare perspective, costs incurred by patients reflected in these evaluations are limited. It is advisable that future economic evaluations reflect the true burden of illness and further consider a more patient-focused design.
- As WTP thresholds may vary between countries, there remains the standard challenge to making recommendations on cost-effectiveness in an area with a great deal of variability.
- As insurance coverage in the United States for fertility treatment and medications is not standardly applied and varies drastically depending on policy and location, this presents country-specific challenges deserving further consideration in future evaluations.

Key Takeaways

Economic evaluations of pharmaceutical agents in fertility medicine exhibit large variability with respect to design and focus. Most studies aimed to draw conclusions on cost savings or effectiveness, but it is clear that further standardization and a broadened perspective within these evaluations is necessary for reliable and generalizable recommendations to be made.

References

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