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Review

Sterility, an Overlooked Health Condition

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Abstract: Clinically, infertility is defined as the inability to conceive after a certain period. In contrast, sterility is defined as the inability to produce a biological child; however, this is not a practical definition that can be applied in a clinical setting to a patient's diagnosis. Unlike infertility, sterility is rarely discussed in biomedical and clinical literature and is often used synonymously with infertility. Infertility affects about 10% of couples globally, but the prevalence of sterility remains unknown. We divide sterility into three subtypes natural, clinical, and hardship. To estimate sterility prevalence, we analyzed primary literature and meta-analysis papers on the rates of live births and pregnancies throughout several treatments of infertile couples (e.g., untreated patients, in vitro fertilization-treated, and patients administered other treatments). This analysis indicates that all treatments fail in delivering a biological child to most couples, suggesting that most infertile couples may fail to conceive. More comprehensive primary studies are needed to provide a precise estimate of sterility. Furthermore, research is needed to study the causes of sterility, as well as develop methods for diagnosis and treatment that are financially affordable and emotionally tolerable. Altogether, sterility is an under-discussed condition that is more common than expected, as many infertile couples are unable to conceive and are, in effect, sterile.

Keywords: sterility; sterility prevalence; reproductive futility; infertility; gynecology; andrology; childlessness

1. Introduction

Sterility is a condition of involuntary childlessness. In contrast, infertility is a condition of having difficulty conceiving [1]. Sterility is a devastating and life-changing condition that also affects mental health [2–8]. Unsuccessful infertility treatment is common, but how common is unclear. The realization of sterility and the emotional transition to involuntary childlessness can take its toll on the couple [9–12]. Even with donor oocytes or donor insemination, mixed emotional responses make this an unideal treatment option [13–16].

The field of reproductive medicine has established protocols that clinicians follow to diagnose, manage, and treat infertile couples that are published by various well-respected societies and organizations [17–26]. For the couples that seek treatment, the male and female should be seen together by the clinician to make an accurate evaluation. They should be counseled on the definition of infertility, factors that contribute to infertility, as well as principles of infertility care. The clinician can also offer an option to investigate further why the couple is experiencing infertility. This investigation would include male and female workup. Based on the diagnosis, three main types of fertility assistance can be offered, such as medical treatment, surgical treatment, or assisted reproductive technology

(i.e., in vitro fertilization (IVF) or Intracytoplasmic sperm injection (ICSI)). In general, these documents do not name sterility as a diagnosis. Sterility is only discussed in the context of oocyte donation in ovulation disorders and donor insemination in non-obstructive azoospermia and severe deficits in semen quality.

In this review, we aim to shed light on the gaps in knowledge and the future directions of sterility research. We point out that "sterility" lacks a practical definition, and we define it as the inability to conceive due to natural, clinical, or hardship reasons, which can be applied to both prospective and retrospective determinations of the condition (Section 1). We also emphasize that there is currently no available test to diagnose patients with clinical sterility (i.e., no prospective determination) (Section 2). A reliable analysis of sterility prevalence is unavailable. We estimate it by reviewing papers on live births without treatment (since most couples do not seek treatment), as well as failed live birth rates in patients treated with varicocele repair, intrauterine insemination (IUI), or IVF (i.e., via retrospective determination). When estimating sterility prevalence, we provide a general statement because the estimation is based on small studies, and further investigation is needed to give a specific number (Section 3). We highlight the importance of understanding sterility for patients, physicians, and researchers (Section 4). Finally, we then address other factors such as economic, physical, and psychological burdens that cause patients to discontinue treatment, thereby increasing sterility prevalence (Section 5). We focus on the failure rate of treatment through this discussion, aiming to bring more awareness to sterility and its surprisingly high prevalence. This paper focuses on involuntary sterility and does not include surgical sterility (information about the latter is available [27,28]).

2. There Is a Need to Diagnose Sterility Prospectively

Sterility and infertility are used interchangeably in many papers, leading to confusion on their distinct meaning [29–35]. However, few articles have proposed a distinction between the two terms [36–42]. Most articles define sterility as "the inability to conceive a child." In contrast, infertility is defined as "the inability to produce a live child after one year of attempting to do so" [36–39,41]. Other sources discuss sterility by using the term "involuntarily childless" [43–49]. Few definitions further specify that sterility is the inability to have biological children through natural means [40,42]. This specification is a crucial supplement that considers the measurable ability of medical intervention to overcome sterility conditions. As the differences in definitions need better clarity, we propose that there is a need to universally differentiate *natural sterility* from *clinical sterility* to highlight the chances of treatment success. *Natural sterility* is the couple's physiological inability to conceive a child without medical intervention (i.e., "natural means"). *Clinical sterility* is the couple's physiological inability to conceive a child even after medical intervention, including surgical intervention. Clinical sterility is a subtype of natural sterility, in that clinical sterility is natural sterility for which treatment of the patient will not result in conception. It also appears that a fraction of clinically sterile couples is unable to take advantage of available treatments due to extraneous factors such as economic, psychological, or physical factors. We propose to call this *Hardship sterility*, a term we coined for this type of sterility (Figure 1). Both clinical sterility and hardship sterility can be reduced dramatically by developing new and improved reproductive treatments.

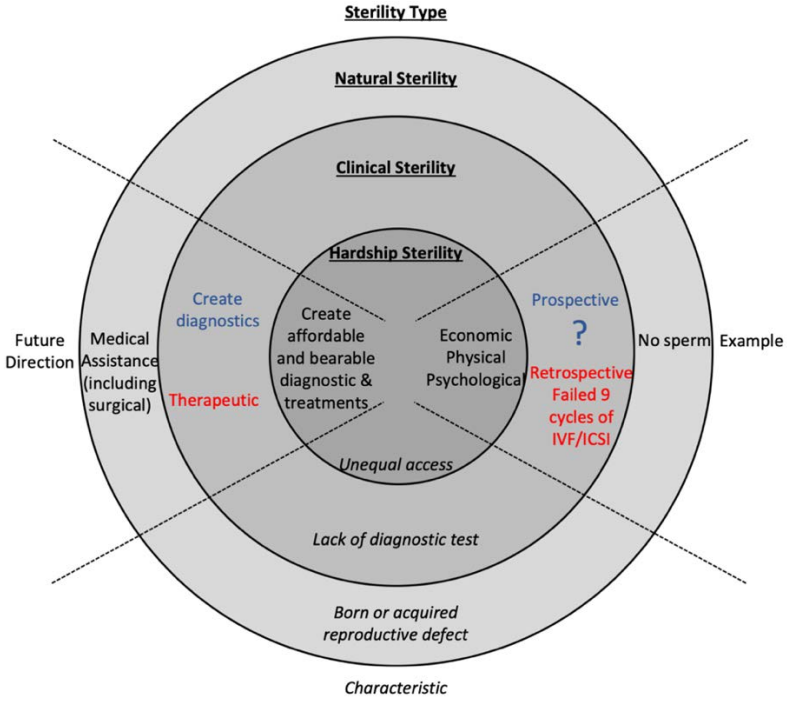

Figure 1. Categories of Sterility include Natural Sterility, Clinical Sterility, and Hardship Sterility. Natural sterility is the couple's physiological inability to conceive a child without medical intervention, an example being someone with no sperm (right), a characteristic is an innate or acquired reproductive defect (bottom), and medical assistance (left) can be used to correct this abnormality. Clinical sterility is the couple's physiological inability to conceive a child even after a medical intervention. An example characteristic of prospective clinical sterility is unable to be determined (blue right), due to the lack of a diagnostic test (bottom), which calls for the creation of diagnostic tests (blue left). An example characteristic of retrospective clinical sterility is a couple that failed nine cycles of in vitro fertilization / Intracytoplasmic sperm injection (IVF/ICSI) (red right). Therapeutic strategies to correct clinical sterility are needed (red left). Hardship sterility, identifies couples who cannot take advantage of available treatments due to economic, psychological, or physical reasons, caused by economic, physical, and psychological factors (right), and its characteristic is unequal access to treatment (bottom). Hardship sterility can be alleviated by devising affordable and tolerable fertility treatments (left).

Future research has two challenges associated with diagnosing natural sterility and clinical sterility that need to be addressed. (i) The term sterility is used qualitatively, and a patient is either sterile or fertile. This qualitative usage hinders sterility determination, as a couple could have a low or meager chance of conceiving rather than no chance at all, as the term "sterility" is defined. A much better approach would be to define sterility quantitatively and as part of a hierarchy ranging from fertility to sterility. Indeed, the Ethics Committee of the American Society of Reproductive Medicine (ASRM) coined the term "futility" to describe fertility treatments that have 1% or less chance of achieving a live birth [50]. (ii) Prospectively diagnosing clinical sterility is challenging, while natural sterility can be determined prospectively by routine diagnostic tests and includes a lack of sperm cells or oocytes. This is due to current technology that allows most natural sterility conditions to be treated, facilitating conception in some patients. These conditions include but are not limited to impotence, structural abnormalities in the male or female reproductive tract, endometriosis [51,52], lack of sperm in the ejaculate (azoospermia) [53,54], ovarian failure [55,56], and varicoceles [57,58].

As a first step towards overcoming the challenges associated with handling sterility in the clinic, we propose to extend the fertility hierarchy proposed by the World Health Organization [59]. The extended hierarchy ranges from fertile, infertile, prospectively clinically sterile, and retrospectively clinically sterile, which is derived from the concept of reproductive futility (Figure 2). According to

the World Health Organization, a *fertile couple* conceives naturally within one year of trying, and an *infertile couple* fails to conceive naturally within one year of trying. The two extensions are elaborations of the "futility" concept proposed by the Ethics Committee of the American Society of Reproductive Medicine (ASRM) [50]. The first extension adds the definition of a *prospectively clinically sterile couple*, who has 1% or less chance of achieving a live birth with reproductive medicine assistance. The second extension introduces a *retrospectively clinically sterile* couple, who have 1% or less chance of achieving a live birth after failing multiple levels (tiers) of reproductive medical assistance. For these definitions to be employed, researchers need to develop diagnostic tests that provide sufficient quantitative information regarding conception chances. It would be essential to have cutoff values that distinguish infertility (a condition that can be treated) from sterility (a condition that most likely will not be treated).

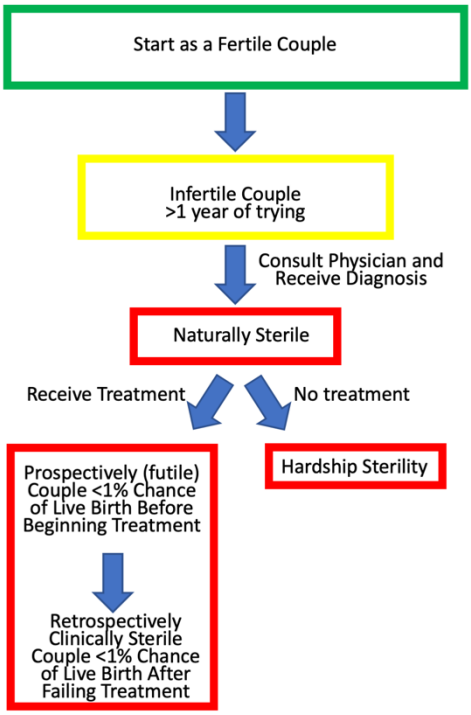

Figure 2. A Fertility Hierarchy ranges from Fertile, Infertile, Prospectively Clinically Sterile, to Retrospectively Clinically Sterile. The fertility hierarchy starts with a fertile couple. If natural conception does not occur within one year of trying, the couple will be identified as an infertile couple. The infertile couple consults with a physician and undergoes a diagnostic test, such as a semen analysis to test for natural sterility. A naturally sterile couple then has the choice of undergoing treatment or not. If they are unable or unwilling to undergo treatment, they are considered to have hardship sterility. A naturally sterile couple that chooses to receive treatment may be identified as prospectively clinically sterile or retrospectively clinically sterile. See more detail in the text.

A second step for overcoming the challenges associated with handling sterility is the development of cutoff values for existing tests and new diagnostic tests for determining sterility prospectively. An example is having cutoff-values for DNA quality that have no realistic chance of producing an offspring [60]. New diagnostic tests may include examining essential sperm structures that currently do not have diagnostic tests, such as the centrioles [61]. Ultimately, it would be useful to develop a comprehensive functional test for sperm that is ethical (not involved in destroying human embryos) and economical. Another approach would be the development of a multi-parametric analysis of the sperm [62]. Developing such diagnostic tools would potentially spare many couples the cost and hardship associated with treatment as well as provide couples with more accurate information regarding their chances of conception, which may assist in their decision to undergo treatment [63].

An attempt to determine futility conditions was made by the Ethics Committee of the ASRM. Their suggestions for treatment of futility highlighted challenges associated with determining futility and sterility prospectively [50]. For example, they suggested that it is futile to treat couples with IVF if a female has an ovarian failure. However, a futility diagnosis seems inappropriate in this case, as multiple studies indicate the success of treatment is as high as 21% under these conditions [55,64,65]. Another example in which futility was determined involved a male partner who lacked viable spermatozoa. A determination of futility is also inappropriate because multiple studies indicate that treatment chances can be as high as 25% and 36% [66–68]. Another example involved a couple who underwent numerous IVF cycles without adequate egg production, fertilization, or embryo development. This example represents a retrospective determination of futility, as prospectively, the chances of success appear to be more than 1% and are around 4–5% [69]. As shown, none of these scenarios included a 1% or less chance of achieving a live birth, and therefore cannot be considered to determine futility.

3. Most Treatments of Infertile Couples Fail to Deliver a Live Birth

One of the main challenges in studying sterility is a lack of reliable sources for the prevalence of sterility among infertile couples. One small cross-sectional study which consisted of 116 people found that ~4% of all couples remain involuntarily childless [70]. Multiple studies examine women who are involuntarily childless and suggest that, on average, 3.9% of females are sterile [37,43–49] (Table 1). In contrast, the prevalence of male sterility is rarely provided, although the general prevalence of male childlessness is high (12–40%) [71,72]. From these prevalence rates, it is impossible to estimate involuntarily childlessness in infertile couples accurately, but it appears to be higher than 4%.

Table 1. The average estimated prevalence of involuntary sterility in females is about 3.9%, but can range from 1–10%.

Total Population	Involuntarily Childless Prevalence	Method	Location	Year(s)	Study
N/A	1–5% of women *	Data Analysis [1]	N/A	N/A	[37]
N/A	2.1% of women	Surveys	USA	2011–2015	[43]
N/A	1–9% of women **	Data Analysis [2]	USA	1982, 1988, 1995, 2002	[44]
3141	3% of women	Surveys	UK	1993	[45]
1574	3% of women	Data Analysis [3]	UK	1990	[46]
N/A	5–10% of women	Data Analysis [4]	N/A	N/A	[47]
N/A	3.6% of women	Data Analysis [5]	Iran	2010	[48]
	3.9%				Average

The most common method used is data analysis of multiple sources and surveys. Rowland et al. was not included in the table because it estimated prevalence for women born between 1851–1957 and was related to marital status. * Involuntary childlessness prevalence based on women aged 25–35. ** Involuntary childlessness prevalence based on multiple women aged 35–44. [1] Leridon et al., created their own predictive model based on previous literature, which can be found within the reference. Their model analyzed sterility prevalence per 1000 different aged married women. [2] National Survey of Family Growth results from 1982, 1988, 1995, and 2002 were compiled and analyzed. [3] A compilation of questionnaires, medical record searches, and interviews were collected from 872 women from a general practice and 702 hospital patients. [4] Kreyenfeld et al. based the prevalence rate on three other literary sources, which can be found within the reference. [5] Department of Homeland Security Report from 2011 was analyzed.

We assessed sterility by combining information on live birth rates and pregnancies in infertile couples. Infertile couples can be divided into two main groups based on the treatment they receive: (i) Not treated; this is the largest group, comprising 64–78% of infertile couples [73] and (ii) Treated by IUI, varicocele repair, or IVF/ICSI.

3.1. Untreated Infertile Couples

The proportion of infertile couples that do not receive clinical treatments is surprisingly high. A meta-analysis of four studies that included a total of 1846 patients in developed countries (e.g., the United Kingdom, France, and the United States) determined that only 22.4% of infertile

couples received treatment for infertility [73]. According to a more recent study of the National Survey of Family Growth in the United States, only 36% of infertile couples ages 25–44 used infertility services during 2006 to 2010 [74]. These data suggest that most infertile couples (64%) are untreated for infertility.

The rates of pregnancies and live births in untreated infertile couples between the years 1979 and 2018 were analyzed in nine papers, comprising a total of **3770 couples** [75–85] (Table 2). Most infertile couples (weighted average of 70%) failed to conceive or have a biological child. The main medical factors that contributed to childlessness were unexplained infertility, endometriosis, cervical, tubal, ovulatory, and seminal defects. Altogether, these findings suggest that most infertile couples that do not undergo fertility treatment do not conceive.

Table 2. The estimated sterility prevalence for infertile couples that go untreated is 70%. These studies from different locations summarize how many live births and pregnancies were achieved without treatment. We calculated the weighted average (((N1*%1) + (N2*%2) + (N . . . *%...))/(N1+N2+N . . .)) for the nine studies.

Number of Patients	Successful Pregnancy/Live Birth	Treatment Failure	Location	Study
654	343 live births	48%	Australia	[75]
107	35 pregnancies	67%	Netherlands	[76]
548	191 live births	65%	United States	[77]
108	28 pregnancies	74%	United States	[78]
16	4 pregnancies	75%	United States	[79]
126	27 pregnancies	78%	United Kingdom	[80]
100	14 pregnancies	86%	Germany	[81]
817	54 live births	93%	Denmark	[82]
100	9 live births	91%	New Zealand	[83]
98	42 pregnancies	57%	Bosnia and Herzegovina	[84]
1096	386 pregnancies	65%	Denmark	[85]
Total: 3770		70%		Weighted Average

3.2. Treated Infertile Couples

Here, we discuss several fertility treatments: varicocele surgery, IUI, and ICSI. Varicocele surgery is a common treatment provided to one-third of male infertility cases [86]. An older meta-analysis paper that included seven studies totaling 281 couples between 1979 and 2001 estimated that 78% of infertile couples treated with varicocele repair were unable to produce a live birth [87]. Seven other papers analyzed 594 couples between the years 1998 and 2019 [88–94] (Table 2). In all studies, most infertile couples failed to deliver a biological child (78%, 67%, 81%, 50%, 90%, 79%, and 75%) with a weighted average of 69%. All of these studies reported pregnancies, and therefore, the actual prevalence of sterility in this group is likely to be higher. Some factors contributing to unsuccessful pregnancies after varicocele repair included lower sperm count and longer infertility duration before surgery and immotile sperm after surgery.

IUI is a well-known infertility treatment that should be administered before IVF in most protocols [95,96]. The National Survey of Family Growth reported that 7.4% of infertile couples aged 25–44 underwent IUI in 2006–2010 [74]. Between the years 1993 and 2016, eight papers estimated the rate of live births among 15,172 couples who underwent IUI treatment [82,83,97–101] (Table 3). In all these studies, most infertile couples failed to deliver a biological child (66%, 79%, 79%, 62%, 81%, 78%, 90%, and 69%) with a weighted average of 69%. Similar factors that prevented untreated infertile couples from spontaneously conceiving contributed to unsuccessful live births in IUI treated couples. These factors also included unexplained infertility, endometriosis, and cervical, tubal, ovulatory, or seminal defects.

Table 3. The estimated sterility prevalence for couples that undergo intrauterine insemination (IUI) and Varicocele Repair is 69%.

Patient Number	Treatment:	Successful Pregnancy/Live Birth	Treatment Failure	Location	Study
281	Varicocele Repair	61 pregnancies	78%	N/A	[87]
145	Varicocele Repair	66 pregnancies	54%	China	[88]
73	Varicocele Repair	24 pregnancies	67%	N/A	[89]
78	Varicocele Repair	15 pregnancies	81%	USA	[90]
148	Varicocele Repair	74 pregnancies	50%	China	[91]
10	Varicocele Repair	1 pregnancy	90%	USA	[92]
120	Varicocele Repair	25 pregnancies	79%	Turkey	[93]
20	Varicocele Repair	5 pregnancies	75%	USA	[94]
Total: 857			69%		Weighted Average
12,488	IUI	4271 live births	66%	Denmark	[97]
533	IUI	111 live births	79%	USA	[98]
456	IUI [1]	96 live births	79%	Turkey	[99]
133	IUI	50 live births	62%	France	[100]
475	CC/IUI	92 live births	81%	USA	[101]
169	FSH/IUI	37 live births	78%	USA	[101]
817	IUI	81 live births	90%	Denmark	[82]
101	IUI [2]	31 live births	69%	New Zealand	[83]
Total: 15,172			69%		Weighted Average

These studies from different locations summarize how many live births and pregnancies were achieved through these treatments. [1] with recombinant gonadotrophin stimulation, [2] with ovarian stimulation. We calculated the weighted average: (((N1*%1) + (N2*%2) + (N . . . *%...))/(N1 + N2 + N . . .)) for each of the eight studies. N, patient number, FSH, the treatment included Follicle-stimulating hormone. CC, the treatment included clomiphene citrate.

The National Survey of Family Growth reported that 3.1% of women aged 25–44 utilized ART, making it the lowest used infertility service [74]. The Society for Assisted Reproductive Technology report for 2017 states that a total of 72,253 new and 45,472 continuing female patients underwent IVF with their own oocytes. This is equal to 0.07% and 0.12% of 60,800,000 married couples in the USA in 2017. Assuming an infertility rate of 12–15.5% in the USA, this is calculated to 0.84–1.09% and 1.44–1.86% of infertile patients utilizing IVF in 2017 [74,102]. In total, 3.1% or less of infertile women undergo IVF.

Five high-quality studies traced the cumulative live birth rate success over many IVF cycles with large cohorts of patients [69,103–106]. These studies were conducted in the United States, the United Kingdom, Australia, and New Zealand over two decades (1990–2012) and each study involved 56,652 to 178,898 females. Two of these studies (Smith et al., 2015 and Stern et al., 2008) included women who used donor oocytes. The use of donor oocytes increases the chance of success in some cases but does not always result in a biological child [107]. Therefore, we have excluded pregnancies resulting from donor oocytes from our analysis. In four of these studies [103–106], the statistics used to calculate the cumulative live birth rate were split into optimistic or conservative estimations. The conservative calculation assumed that women who stopped receiving treatment would not have any live births, which aligns with the clinic's results. The optimistic calculation assumed that women who stopped receiving treatment would have the same chance of conceiving as those who continued. While the optimistic calculation demonstrates the potential of ICSI to produce live births in an ideal scenario, it is not realistic when considering real-life conditions (see discussion below on hardship sterility); therefore, we used the conservative estimates here. Based on all conservative estimates and excluding donor oocyte treatment, sterility prevalence percentages are 67%, 56%, 49%, 49%, 46%, and 47% in the ICSI group (Figure 3).

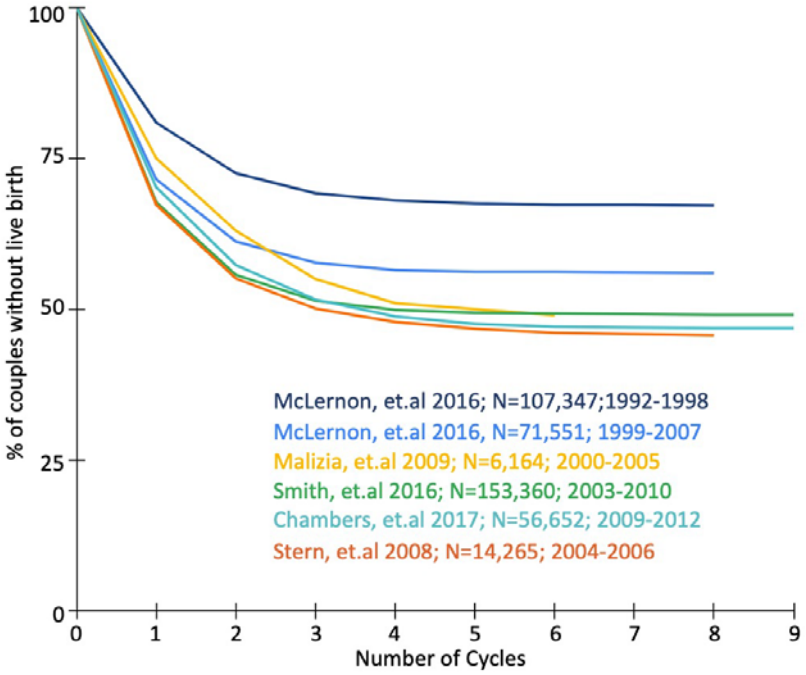

Figure 3. ICSI failed to result in a live birth in more than 47% treated infertile couples. The conservative estimate of the cumulative live birth rate per cycle was calculated assuming that women who discontinued treatment would have no chance of achieving a live birth. McLernon et al. (2016) was split into two time periods. Smith et al. (2015) used a calculation that did not include women who used donor oocytes but was split by age category, so the results for women below the age of 40 were used. Our calculation included women of all ages, with a mean age of 33–35 years old. References: [69,103–106].

The information found in the literature on sterility did not allow us to determine a precise prevalence rate. However, based on the literature reviewed above and assuming that the infertile couples in these studies did not receive additional treatments, we estimate that many, if not most, infertile couples are sterile (Figure 4).

We considered the following five points:

(1) 10% of couples are infertile couples, and more than 4% are involuntarily childless or sterile;
(2) At the least, 64% of infertile couples are not treated, and 70% of them fail to have a live birth;
(3) 7.4% of infertile couples undergo IUI, and 69% of them fail to have a live birth;
(4) ~33% of infertile men undergo varicocele treatment, and 69% of them fail to have a live birth;
(5) ~3.1% of infertile women undergo ICSI, and 47% of them fail to have a live birth.

Based on this information, we consider the sterility rate to be within a range. The lowest sterility prevalence rate limit is 40% of infertile couples (Point 1 above). The highest limit was calculated by a weighted average of points 2–5 above and results in 76% of infertile couples being sterile. More research is needed for a precise estimate.

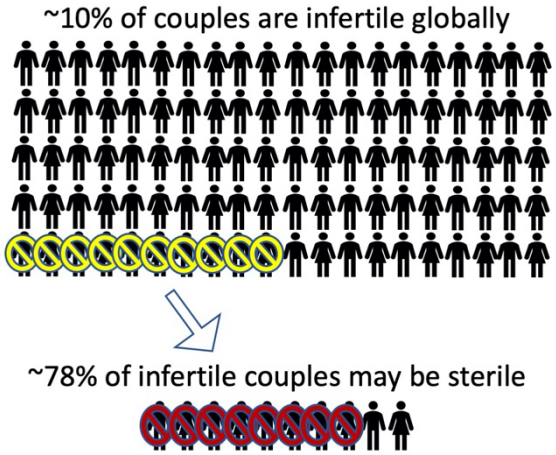

Figure 4. Ten percent of Couples throughout the world are infertile, and as many as 76% of them may be Sterile.

4. Understanding Sterility Will Benefit the Patient, Physician, and Researchers

An understanding of sterility will benefit the patient, physician, and researchers. *Patients* will benefit from knowing their condition regarding sterility in two main ways. Firstly, understanding the prevalence of sterility will enable couples to make better-informed decisions when seeking treatment after being diagnosed with infertility. Secondly, a full understanding of a sterility diagnosis can save couples time and money and spare them from invasive treatments and unnecessary frustration. They may also be encouraged to seek non-biological children using donor oocytes, donor sperm, surrogacy, or adoption.

Physicians treating patients will benefit from understanding sterility and its prevalence in two main ways. Firstly, it will help the physician to remain ethical. According to the Ethics Committee of the American Society of Reproductive Medicine, it is unethical to continue treatments if patients are not fully educated about the probability of a successful birth [50]. With proper education, however, it remains the choice of the patient to continue treatment or not. Secondly, this understanding will contribute to physician credibility, as it will enable them to make the most accurate treatment recommendation aimed at achieving the most successful fertility outcome.

Researchers will benefit from a greater understanding of sterility and its prevalence. Firstly, the surprisingly high prevalence of sterility will encourage more in-depth research on the cause of clinical sterility where treatment is unavailable. Secondly, this research could lead to the determination of official cut of values for clinical sterility to existing diagnostic tests (which currently only few specific sperm properties) and the development of comprehensive functional and multiparametric diagnostic tools, as well as the eventual development of therapeutics.

Ultimately, these positive outcomes will benefit treatment-seeking patients, as they will lead to personalized treatment plans specifically tailored to their situation.

5. Economic, Physical, and Psychological Burdens Contribute to Hardship Sterility

Economic, physical, and psychological burdens contribute to reduced fertility. It was estimated that 2.5% of women in the USA were childless because of poverty and 8.1% because of high cost of childrearing [108]. Consequentially, not all infertile patients seek fertility treatments due to the associated high costs and the physical and psychological burdens, resulting in hardship sterility. In the United States, the average cost for IVF treatment in 2001 was $9226 per IVF cycle and $56,419 for a live birth [109]. In 2006, the average cost of one IVF cycle was $12,513, while the cost of live birth was $41,132 [110]. In 2011, the average cost of IVF resulting in a live birth was $61,377 [111]. It is reasonable, then, that the cost of IVF treatment plays a major role in couples' decisions to discontinue treatment [112].

A systematic analysis that reviewed 22 studies with 21,453 patients from 8 different countries found that 15.32% of patients decided not to continue treatment during the diagnostic phase because of the cost, while 9.19% overall discontinued due to financial reasons [112]. Additional major reasons reported by patients for discontinuing fertility treatments included treatment postponement (39.18%), relational and personal problems (16.67%), and the psychological (14%) and physical (6.32%) health of the female partner or couple [112].

Another study surveyed patients who possessed insurance coverage for three IVF cycles but still discontinued treatment. Of the 47 patients that responded, 39% blamed stress as the reason for dropping out of treatment [113]. This indicates that the psychological turmoil associated with fertility treatments caused some couples to choose to discontinue treatment, thereby contributing to sterility prevalence. This also suggests that improving the efficiency of treatments may encourage more couples to continue treatments, thereby reducing the rate of hardship sterility.

The most optimistic scenario in the ICSI cumulative live birth rate studies showed that only 10.6% of couples were left without a child after undergoing nine fertility treatments (Figure 5). This indicates that if couples can endure nine treatments, their chances of having a child increase significantly, demonstrating the potential of ICSI. It is possible to significantly decrease the sterility rate if the efficiency of fertility treatments is improved [104]. For example, the use of a surrogate improves the chance of having a live birth, but surrogacy is a costly option that is not widely used [114]. Since only ~3.1% of infertile people undergo ICSI, and 78% do not seek treatment, the real potential of having a child with ICSI is unclear.

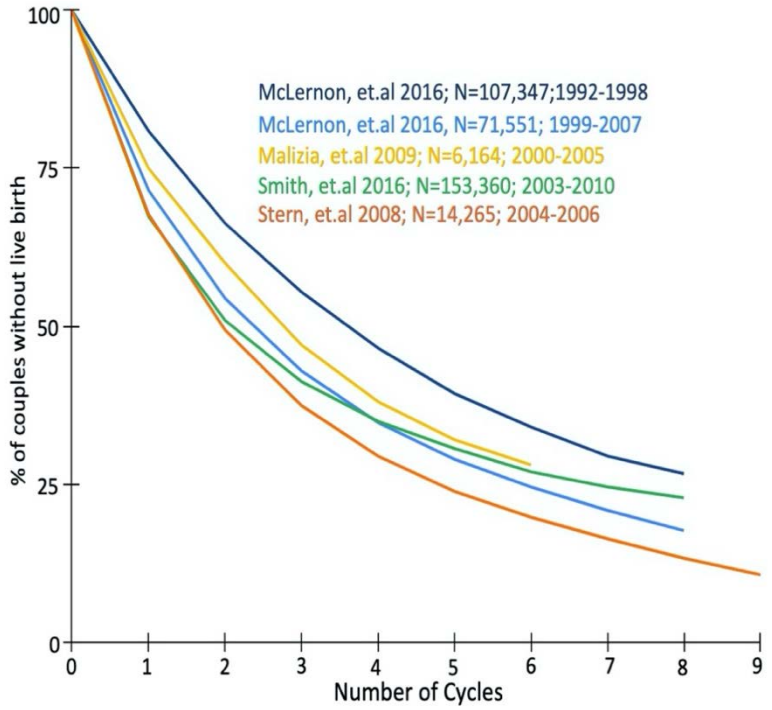

Figure 5. If Women Do Not Dropout from ICSI Treatment, It Is Predicted to Fail to Result in a Live Birth Only in 11% of Couples. The optimistic estimate was calculated assuming women who discontinued IVF treatment would have a chance to achieve a live birth similar to that of women who remained in treatment. McLernon et al. (2016) was split into two time periods. Smith et al. (2015) used a calculation that excluded women who used donor oocytes, but was split by age category, so the results for women below the age of 40 were used. Stern et al. (2008) did not calculate an optimal estimate, so it was not included. Our calculation included women of all ages, with a mean age of 33–35 years old. Using the optimal estimate's best-case scenario, 10.6% of women will be left without a child after treatment. References: [103–106].

6. Discussion

Based on the above information, it is likely that the prevalence of sterility is significantly high, and about 40–76% of infertile couples are sterile. In this study, we highlight the need to investigate this thoroughly and conclusively in the future. Although there is a major difference between sterility and infertility, much remains unknown about sterility due to a lack of clinical literature on the topic. The reason for this lack of literature on female and male sterility is unclear; perhaps the topic is not commonly discussed due to the stigma associated with the term. For example, patients, whether female or male, might be more distressed with a diagnosis of sterility than with one of infertility. On the same note, it may be that a diagnosis of sterility may exacerbate psychological problems and lead to other social issues for some patients.

Due to the lack of information available on sterility, no prospectively functional definition exists. Although many fertility experts intuitively differentiate between natural sterility and clinical sterility, there is currently no official recognition of the differences between them. Another important deficiency is the absence of official cutoff values to diagnose sterility and a more comprehensive test to predict sterility confidently. Possible routes to accomplish this are to develop multi-quantitative parametric tests that use many aspects of reproductive biology and provide an estimate the chance to conceive with current treatment or to develop a comprehensive functional test.

Additionally, the invasive and expensive nature of IVF/ICSI treatment causes many patients to discontinue treatment, which further contributes to sterility prevalence. It is important to include in the discussion that reproductive treatment is affected by extraneous factors such as finance. Therefore, it is important to intensify discussions on sterility and sterility prevalence as well as to direct research toward the development of clinical sterility diagnostic tools.

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Glossary

Clinical Sterility	The physiological inability of a couple to conceive a child even after medical intervention, including surgical intervention.
Clinically Sterile Couple	A couple with 1% or less chance of achieving a live birth with reproductive medicine assistance.
Cumulative Live Birth Rate	A couple's chance to have a live birth after cumulative cycles of fertility treatment.
Fertile Couple	A couple that conceives naturally within one year of trying.
Hardship Sterility	The physiological inability of a couple to conceive a child even after medical intervention because of economic, psychological, or physical reasons.
ICSI	Intracytoplasmic sperm injection; a fertility procedure in which sperm is injected into an egg.
Infertility	A difficulty to conceive that is defined in most cases as the inability to conceive a biological child after one year of attempting.
IUI	Intrauterine insemination; a fertility procedure in which sperm is placed inside a female's uterus.

IVF	In-vitro fertilization; a fertility treatment that combines the egg and sperm outside the body, and then the embryo is transferred into the uterus.
Natural Sterility	The physiological inability of a couple to conceive a child without medical intervention (i.e., "natural means").
Prospective Determination	The ability to diagnose a patient with clinical sterility before beginning treatment.
Reproductively Futile Couple	A couple with 1% or less chance of achieving a live birth with reproductive medicine assistance.
Retrospective Determination	The ability to diagnose a patient with clinical sterility after treatments have failed.
Retrospectively Clinically Sterile Couple	A couple with 1% or less chance of achieving a live birth after failing multiple treatments of reproductive medical assistance.
Prospectively Clinically Sterile Couple	A couple with 1% or less chance of achieving a live birth with reproductive medicine assistance.
Sterility	The inability to conceive due to natural, clinical, or hardship factors, determined either prospectively or retrospectively.
Varicocele Repair	Repair of the enlarged veins within the scrotum

References

1. Gurunath, S.; Pandian, Z.; Anderson, R.A.; Bhattacharya, S. Defining infertility–a systematic review of prevalence studies. *Hum. Reprod. Update* **2011**, *17*, 575–588. [CrossRef] [PubMed]
2. Hadley, R.A. 'It's most of my life—going to the pub or the group': The social networks of involuntarily childless older men. *Ageing Soc.* **2019**, 1–26. [CrossRef]
3. Miall, C.E. The stigma of involuntary childlessness. *Soc. Probl.* **1986**, *33*, 268–282. [CrossRef]
4. Van Balen, F.; Trimbos-Kemper, T.C. Involuntarily childless couples: Their desire to have children and their motives. *J. Psychosom. Obstet. Gynaecol.* **1995**, *16*, 137–144. [CrossRef]
5. Schwerdtfeger, K.L.; Shreffler, K.M. Trauma of Pregnancy Loss and Infertility for Mothers and Involuntarily Childless Women in the Contemporary United States. *J. Loss Trauma* **2009**, *14*, 211–227. [CrossRef]
6. Khan, A.R.; Iqbal, N.; Afzal, A. Impact of Infertility on Mental Health of Women. *Int. J. Indian Psychol.* **2019**, *7*, 804–809. [CrossRef]
7. Tyuvina, N.; Nikolaevskaya, A. Infertility and mental disorders in women. Communication 1. *Neurol. Neuropsychiatry Psychosom.* **2019**, *11*, 117–124. [CrossRef]
8. Miner, S.A.; Daumler, D.; Chan, P.; Gupta, A.; Lo, K.; Zelkowitz, P. Masculinity, Mental Health, and Desire for Social Support. Among Male Cancer and Infertility Patients. *Am. J. Men's Health* **2019**, *13*, 1557988318820396. [CrossRef]
9. Roy, R.N.; Schumm, W.R.; Britt, S.L. Voluntary versus involuntary childlessness. In *Transition to Parenthood*; Springer: Berlin, Germany, 2014; pp. 49–68.
10. Biryukova, S.S.; Tyndik, A.O. Prevalence and determinants of childlessness in Russia and Moscow. *Genus* **2015**, *71*, 1–22.
11. Onyedibe, M.-C.C.; Aliche, C.J.; Ugwu, L.E.; Obi-Keguna, C.N.; Nnama-Okechukwu, C.U.; Okoye, U.O.; Iorfa, S.K.; Ifeagwazi, C.M.; Chukwuorji, J.C.; Osamika, B.E. Self-esteem and psychological distress among involuntary childless couples. Moderating roles of coping strategies. *Niger. J. Psychol. Res.* **2019**, *15*, 1–7.
12. Grube, T. A Grounded Theory Approach to Explore the Experience of Involuntary Childlessness in Couples with Infertility. Ph.D. Thesis, Widener University, Chester, PA, USA, 2019.
13. Carter, J.; Applegarth, L.; Josephs, L.; Grill, E.; Baser, R.E.; Rosenwaks, Z. A cross-sectional cohort study of infertile women awaiting oocyte donation: The emotional, sexual, and quality-of-life impact. *Fertil. Steril.* **2011**, *95*, 711–716.e1. [CrossRef] [PubMed]
14. Wischmann, T.; Thorn, P. (Male) infertility: What does it mean to men? New evidence from quantitative and qualitative studies. *Reprod. Biomed. Online* **2013**, *27*, 236–243. [CrossRef] [PubMed]
15. Banerjee, K.; Singla, B. Acceptance of donor eggs, donor sperms, or donor embryos in Indian infertile couples. *J. Hum. Reprod. Sci.* **2018**, *11*, 169. [PubMed]

16. Kerckhof, M.; Van Parys, H.; Pennings, G.; De Sutter, P.; Buysse, A.; Provoost, V. Donor insemination disclosure in social networks: Heterosexual couples' experiences. *Cult. Health Sex.* **2020**, *22*, 292–306. [CrossRef] [PubMed]
17. National Collaborating Centre for Women's; Children's Health. National Institute for Health and Clinical Excellence: Guidance. In *Fertility: Assessment and Treatment for People with Fertility Problems*; Royal College of Obstetricians & Gynaecologists: London, UK, 2013.
18. Practice Committee of the American Society for Reproductive Medicine; Practice Committee of the Society for Assisted Reproductive Technology. Repetitive oocyte donation: A committee opinion. *Fertil. Steril.* **2014**, *102*, 964–966. [CrossRef]
19. Practice Committee of the American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss: A committee opinion. *Fertil. Steril.* **2020**, *113*, 533–535. [CrossRef] [PubMed]
20. Practice Committee of the American Society for Reproductive Medicine. Evidence-based treatments for couples with unexplained infertility: A guideline. *Fertil. Steril.* **2020**, *113*, 305–322. [CrossRef]
21. Practice Committee of the American Society for Reproductive Medicine. Diagnostic evaluation of the infertile female: A committee opinion. *Fertil. Steril.* **2015**, *103*, e44–e50. [CrossRef]
22. Practice Committee of the American Society for Reproductive Medicine. Diagnostic evaluation of the infertile male: A committee opinion. *Fertil. Steril.* **2015**, *103*, e18–e25. [CrossRef]
23. Kamel, R.M. Management of the infertile couple: An evidence-based protocol. *Reprod. Biol. Endocrinol.* **2010**, *8*, 21. [CrossRef]
24. Committee on Gynecologic Practice, American Society for Reproductive Medicine. Infertility Workup for the Women's Health Specialist: ACOG Committee Opinion, Number 781. *Obstet. Gynecol.* **2019**, *133*, e377–e384. [CrossRef] [PubMed]
25. Buckett, W.; Sierra, S. The management of unexplained infertility: An evidence-based guideline from the Canadian Fertility and Andrology Society. *Reprod. Biomed. Online* **2019**, *39*, 633–640. [CrossRef] [PubMed]
26. Warner, L.; Jamieson, D.J.; Barfield, W.D. CDC releases a National Public Health Action Plan. for the Detection, Prevention, and Management of Infertility. *J. Womens Health* **2015**, *24*, 548–549. [CrossRef]
27. Webb, S.; Holman, D. A survey of infertility, surgical sterility and associated reproductive disability in Perth, Western Australia. *Aust. J. Public Health* **1992**, *16*, 376–381. [CrossRef] [PubMed]
28. Hardy, E.; Bahamondes, L.; Osis, M.J.; Costa, R.G.; Faúndes, A. Risk factors for tubal sterilization regret, detectable before surgery. *Contraception* **1996**, *54*, 159–162. [CrossRef]
29. Rubin, I.C.; Zakin, D. Contraception Masking Sterility and Infertility: Tubal and Seminal Factors in 1000 Cases. *J. Am. Med Assoc.* **1946**, *132*, 1047–1053. [CrossRef] [PubMed]
30. Beke, A. Genetic Causes of Female Infertility. In *Genetics of Endocrine Diseases and Syndromes*; Igaz, P., Patócs, A., Eds.; Springer International Publishing: Cham, Switzerland, 2019; pp. 367–383.
31. Popović, J.; Sulović, V.; Vucetić, D. Laparoscopy treatment of adnexal sterility. *Clin. Exp. Obstet. Gynecol.* **2005**, *32*, 31–34. [PubMed]
32. Mettler, L.; Scheidel, P.; Shirwani, D. Sperm antibody production in female sterility. *Int. J. Fertil.* **1974**, *19*, 7–12.
33. Cohen, M.R. Sterility and Infertility-Medical Views. *J. Am. Med Assoc.* **1958**, *168*, 1963–1970. [CrossRef]
34. Macomber, E.R.a.D. *Fertility and Sterility in Human Marriages*; W.B. Saunders Company: Philadelphia, PA, USA, 1924.
35. Guttmacher, A.F. The Role of Artificial Insemination in the Treatment of Human Sterility. *Bull. N. Y. Acad. Med.* **1943**, *19*, 573–591.
36. Eliasson, R. *Analysis of Semen in Comprehensive Endocrinology*; Burger, H.K.D.D.E., Ed.; Raven Press: New York, NY, USA, 1981.
37. Leridon, H. A new estimate of permanent sterility by age: Sterility defined as the inability to conceive. *Popul. Stud.* **2008**, *62*, 15–24. [CrossRef]
38. Egozcue, J.; Templado, C.; Vidal, F.; Navarro, J.; Morer-Fargas, F.; Marina, S. Meiotic studies in a series of 1100 infertile and sterile males. *Hum. Genet.* **1983**, *65*, 185–188. [CrossRef] [PubMed]
39. Rochon, M. Sterility and infertility: Two concepts. *Cah. Que Demogr.* **1986**, *15*, 27–56. [PubMed]
40. Brugo-Olmedo, S.; Chillik, C.; Kopelman, S. Definition and causes of infertility. *Reprod. Biomed. Online* **2001**, *2*, 173–185. [CrossRef]
41. Habbema, J.D.F.; Collins, J.; Leridon, H.; Evers, J.L.H.; Lunenfeld, B.; teVelde, E.R. Towards less confusing terminology in reproductive medicine: A proposal. *Hum. Reprod.* **2004**, *19*, 1497–1501. [CrossRef] [PubMed]

42. Forti, G.; Krausz, C. Evaluation and Treatment of the Infertile Couple1. *J. Clin. Endocrinol. Metab.* **1998**, *83*, 4177–4188. [CrossRef]
43. Show, H.-A.C.D.I.; Decline, S. Prevalence of Infertility and Its Treatment Among Women. *US Pharm.* **2018**, *43*, 14.
44. Abma, J.C.; Martinez, G.M. Childlessness Among Older Women in the United States: Trends and Profiles. *J. Marriage Fam.* **2006**, *68*, 1045–1056. [CrossRef]
45. Gunnell, D.J.; Ewings, P. Infertility prevalence, needs assessment and purchasing. *J. Public Health* **1994**, *16*, 29–35. [CrossRef]
46. Greenhall, E.; Vessey, M. The prevalence of subfertility: A review of the current confusion and a report of two new studies. *Fertil. Steril.* **1990**, *54*, 978–983. [CrossRef]
47. Kreyenfeld, M.; Konietzka, D. Analyzing Childlessness. In *Childlessness in Europe: Contexts, Causes, and Consequences*; Kreyenfeld, M., Konietzka, D., Eds.; Springer International Publishing: Cham, Switzerland, 2017; pp. 3–5.
48. Razeghi-Nasrabad, H.B.; Abbasi-Shavazi, M.J.; Moeinifar, M. Are we facing a dramatic increase in infertility and involuntary childlessness that lead to lower fertility. *Crescent J. Med. Biol. Sci.* **2020**, *7*, 1–14.
49. Rowland, D.T. The prevalence of childlessness in cohorts of older women. *Australas. J. Ageing* **1998**, *17*, 18–23. [CrossRef]
50. Ethics Committee of the American Society for Reproductive Medicine. Fertility treatment when the prognosis is very poor or futile: A committee opinion. *Fertil. Steril.* **2012**, *98*, e6–e9. [CrossRef] [PubMed]
51. Spangler, D.B.; Jones, G.S.; Jones, H.W. Infertility due to endometriosis: Conservative surgical therapy. *Am. J. Obstet. Gynecol.* **1971**, *109*, 850–857. [CrossRef]
52. Tanbo, T.; Fedorcsak, P. Endometriosis-associated infertility: Aspects of pathophysiological mechanisms and treatment options. *Acta Obstet. Gynecol. Scand.* **2017**, *96*, 659–667. [CrossRef]
53. Tournaye, H.; Camus, M.; Goossens, A.; Liu, J.; Nagy, P.; Silber, S.; Van Steirteghem, A.C.; Devroey, P. Recent concepts in the management of infertility because of non-obstructive azoospermia. *Hum. Reprod.* **1995**, *10* (Suppl. 1), 115–119. [CrossRef]
54. Yang, Y.; Guo, J.; Dai, L.; Zhu, Y.; Hu, H.; Tan, L.; Chen, W.; Liang, D.; He, J.; Tu, M. XRCC2 mutation causes meiotic arrest, azoospermia and infertility. *J. Med. Genet.* **2018**, *55*, 628–636. [CrossRef]
55. Schmidt, K.T.; Rosendahl, M.; Ernst, E.; Loft, A.; Andersen, A.N.; Dueholm, M.; Ottosen, C.; Andersen, C.Y. Autotransplantation of cryopreserved ovarian tissue in 12 women with chemotherapy-induced premature ovarian failure: The Danish experience. *Fertil. Steril.* **2011**, *95*, 695–701. [CrossRef]
56. Mohamed, S.A.; Shalaby, S.M.; Abdelaziz, M.; Brakta, S.; Hill, W.D.; Ismail, N.; Al-Hendy, A. Human mesenchymal stem cells partially reverse infertility in chemotherapy-induced ovarian failure. *Reprod. Sci.* **2018**, *25*, 51–63. [CrossRef]
57. Al-Said, S.; Al-Naimi, A.; Al-Ansari, A.; Younis, N.; Shamsodini, A.; A-sadiq, K.; Shokeir, A.A. Varicocelectomy for Male Infertility: A Comparative Study of Open, Laparoscopic and Microsurgical Approaches. *J. Urol.* **2008**, *180*, 266–270. [CrossRef]
58. Lundy, S.D.; Sabanegh, E.S., Jr. Varicocele management for infertility and pain: A systematic review. *Arab J. Urol.* **2018**, *16*, 157–170. [CrossRef] [PubMed]
59. WHO. Sexual and Reproductive Health: Infertility Definitions and Terminology. World Health Organisation: Geneva, Switzerland. Available online: www.who.int/reproductivehealth/topics/infertility/definitions/en (accessed on 27 October 2020).
60. WHO. *WHO Laboratory Manual for the Examination and Processing of Human Semen*; World Health Organisation: Geneva, Switzerland, 2010.
61. Avidor-Reiss, T.; Carr, A.; Fishman, E.L. The Sperm Centrioles. *Mol. Cell. Endocrinol.* **2020**, 110987. [CrossRef] [PubMed]
62. Turner, K.A.; Rambhatla, A.; Schon, S.; Agarwal, A.; Krawetz, S.A.; Dupree, J.M.; Avidor-Reiss, T. Male Infertility is a Women's Health Issue—Research and Clinical Evaluation of Male Infertility Is Needed. *Cells* **2020**, *9*, 990. [CrossRef] [PubMed]
63. Group, C.C.W. The current status and future of andrology: A consensus report from the Cairo workshop group. *Andrology* **2020**, *8*, 27–52.
64. Donnez, J.; Dolmans, M.-M. Transplantation of ovarian tissue. *Best Pract. Res. Clin. Obstet. Gynaecol.* **2014**, *28*, 1188–1197. [CrossRef]

65. Pacheco, F.; Oktay, K. Current success and efficiency of autologous ovarian transplantation: A meta-analysis. *Reprod. Sci.* **2017**, *24*, 1111–1120. [CrossRef]
66. Schlegel, P.N.; Palermo, G.D.; Goldstein, M.; Menendez, S.; Zaninovic, N.; Veeck, L.L.; Rosenwaks, Z. Testicular sperm extraction with intracytoplasmic sperm injection for nonobstructive azoospermia. *Urology* **1997**, *49*, 435–440. [CrossRef]
67. Turunc, T.; Gul, U.; Haydardedeoglu, B.; Bal, N.; Kuzgunbay, B.; Peskircioglu, L.; Ozkardes, H. Conventional testicular sperm extraction combined with the microdissection technique in nonobstructive azoospermic patients: A prospective comparative study. *Fertil. Steril.* **2010**, *94*, 2157–2160. [CrossRef]
68. Eken, A.; Gulec, F. Microdissection testicular sperm extraction (micro-TESE): Predictive value of preoperative hormonal levels and pathology in non-obstructive azoospermia. *Kaohsiung J. Med Sci.* **2018**, *34*, 103–108. [CrossRef]
69. Stern, J.E.; Brown, M.B.; Luke, B.; Wantman, E.; Lederman, A.; Missmer, S.A.; Hornstein, M.D. Calculating cumulative live-birth rates from linked cycles of assisted reproductive technology (ART): Data from the Massachusetts SART CORS. *Fertil. Steril.* **2010**, *94*, 1334–1340. [CrossRef]
70. Lechner, L.; Bolman, C.; van Dalen, A. Definite involuntary childlessness: Associations between coping, social support and psychological distress. *Hum. Reprod.* **2007**, *22*, 288–294. [CrossRef] [PubMed]
71. Miettinen, A. Voluntary or involuntary childlessness? Socio-demographic factors and childlessness intentions among childless Finnish men and women aged 25–44. *Finn. Yearb. Popul. Res.* **2010**, *45*, 5–24. [CrossRef]
72. Parr, N. Childlessness among men in Australia. *Popul. Res. Policy Rev.* **2010**, *29*, 319–338. [CrossRef]
73. Boivin, J.; Bunting, L.; Collins, J.A.; Nygren, K.G. International estimates of infertility prevalence and treatment-seeking: Potential need and demand for infertility medical care. *Hum. Reprod.* **2007**, *22*, 1506–1512. [CrossRef]
74. Chandra, A.; Copen, C.E.; Stephen, E.H. Infertility service use in the United States: Data from the National Survey of Family Growth, 1982–2010. *Natl. Health Stat. Rep.* **2014**, *73*, 1–21.
75. Herbert, D.L.; Lucke, J.C.; Dobson, A.J. Birth outcomes after spontaneous or assisted conception among infertile Australian women aged 28 to 36 years: A prospective, population-based study. *Fertil. Steril.* **2012**, *97*, 630–638. [CrossRef]
76. Steures, P.; van der Steeg, J.W.; Hompes, P.G.A.; Habbema, J.D.F.; Eijkemans, M.J.C.; Broekmans, F.J.; Verhoeve, H.R.; Bossuyt, P.M.M.; van der Veen, F.; Mol, B.W.J. Intrauterine insemination with controlled ovarian hyperstimulation versus expectant management for couples with unexplained subfertility and an intermediate prognosis: A randomised clinical trial. *Lancet* **2006**, *368*, 216–221. [CrossRef]
77. Collins, J.A.; Wrixon, W.; Janes, L.B.; Wilson, E.H. Treatment-Independent Pregnancy among Infertile Couples. *N. Engl. J. Med.* **1983**, *309*, 1201–1206. [CrossRef]
78. Kumar, S.; Awasthi, R.T. Treatment unrelated pregnancies in infertile couples. *Med. J. Armed Forces India* **1999**, *55*, 223–225. [CrossRef]
79. Glass, R.H.; Ericsson, R.J. Spontaneous Cure of Male Infertility. *Fertil. Steril.* **1979**, *31*, 305–308. [CrossRef]
80. Dunphy, B.C.; Kay, R.; Robinson, J.N.; Cooke, I.D. The placebo response of subfertile couples to attending a tertiary referral centre **Supported by a Harris Birthright Grant, Royal College of Obstetricians and Gynaecologists, London, United Kingdom. *Fertil. Steril.* **1990**, *54*, 1072–1075. [CrossRef]
81. De Cicco, S.; Tagliaferri, V.; Selvaggi, L.; Romualdi, D.; Di Florio, C.; Immediata, V.; Lanzone, A.; Guido, M. Expectant management may reduce overtreatment in women affected by unexplained infertility confirmed by diagnostic laparoscopy. *Arch. Gynecol. Obstet.* **2017**, *295*, 427–433. [CrossRef] [PubMed]
82. Pinborg, A.; Hougaard, C.O.; Nyboe Andersen, A.; Molbo, D.; Schmidt, L. Prospective longitudinal cohort study on cumulative 5-year delivery and adoption rates among 1338 couples initiating infertility treatment. *Hum. Reprod.* **2009**, *24*, 991–999. [CrossRef] [PubMed]
83. Farquhar, C.M.; Liu, E.; Armstrong, S.; Arroll, N.; Lensen, S.; Brown, J. Intrauterine insemination with ovarian stimulation versus expectant management for unexplained infertility (TUI): A pragmatic, open-label, randomised, controlled, two-centre trial. *Lancet* **2018**, *391*, 441–450. [CrossRef]
84. Hajder, M.; Hajder, E.; Husic, A. The effects of total motile sperm count on spontaneous pregnancy rate and pregnancy after IUI treatment in couples with male factor and unexplained infertility. *Med. Arch.* **2016**, *70*, 39. [CrossRef]

85. Van Eekelen, R.; van Geloven, N.; van Wely, M.; McLernon, D.J.; Mol, F.; Custers, I.M.; Steures, P.; Bhattacharya, S.; Mol, B.W.; van der Veen, F.; et al. Is IUI with ovarian stimulation effective in couples with unexplained subfertility? *Hum. Reprod.* **2018**, *34*, 84–91. [CrossRef] [PubMed]
86. Cocuzza, M.; Cocuzza, M.A.; Bragais, F.M.P.; Agarwal, A. The role of varicocele repair in the new era of assisted reproductive technology. *Clinics* **2008**, *63*, 395–404. [CrossRef]
87. Evers, J.L.H.; Collins, J.A. Assessment of efficacy of varicocele repair for male subfertility: A systematic review. *Lancet* **2003**, *361*, 1849–1852. [CrossRef]
88. Peng, J.; Zhang, Z.; Cui, W.; Yuan, Y.; Song, W.; Gao, B.; Xin, Z.; Zhu, S. Spontaneous pregnancy rates in Chinese men undergoing microsurgical subinguinal varicocelectomy and possible preoperative factors affecting the outcomes. *Fertil. Steril.* **2015**, *103*, 635–639. [CrossRef]
89. Abdel-Meguid, T.A.; Al-Sayyad, A.; Tayib, A.; Farsi, H.M. Does Varicocele Repair Improve Male Infertility? An. Evidence-Based Perspective from a Randomized, Controlled Trial. *Eur. Urol.* **2011**, *59*, 455–461. [CrossRef]
90. Matthews, G.J.; Matthews, E.D.; Goldstein, M. Induction of spermatogenesis and achievement of pregnancy after microsurgical varicocelectomy in men with azoospermia and severe oligoasthenospermia. *Fertil. Steril.* **1998**, *70*, 71–75. [CrossRef]
91. Ren, W.; Qu, J.; Xue, B.; Hu, J.; Zu, X. Infertility duration and pre-operative sperm progressive motility are significant factors of spontaneous pregnancy after varicocele repair. *Am. J. Reprod. Immunol.* **2020**, e13318. [CrossRef]
92. Dubin, J.M.; Greer, A.B.; Kohn, T.P.; Masterson, T.A.; Ji, L.; Ramasamy, R. Men with Severe Oligospermia Appear to Benefit From Varicocele Repair: A Cost-effectiveness Analysis of Assisted Reproductive Technology. *Urology* **2018**, *111*, 99–103. [CrossRef] [PubMed]
93. Çayan, S.; Akbay, E. Fate of Recurrent or Persistent Varicocele in the Era of Assisted Reproduction Technology: Microsurgical Subinguinal Redo Varicocelectomy Versus Observation. *Urology* **2018**, *117*, 64–69. [CrossRef] [PubMed]
94. Masterson, T.A.; Greer, A.B.; Ramasamy, R. Time to improvement in semen parameters after microsurgical varicocelectomy in men with severe oligospermia. *Can. Urol. Assoc. J.* **2019**, *13*, E66–E69. [CrossRef]
95. Bahadur, G.; Homburg, R.; Muneer, A.; Racich, P.; Alangaden, T.; Al-Habib, A.; Okolo, S. First line fertility treatment strategies regarding IUI and IVF require clinical evidence. *Hum. Reprod.* **2016**, *31*, 1141–1146. [CrossRef]
96. Tjon-Kon-Fat, R.I.; Bensdorp, A.J.; Scholten, I.; Repping, S.; van Wely, M.; Mol, B.W.J.; van der Veen, F. IUI and IVF for unexplained subfertility: Where did we go wrong? *Hum. Reprod.* **2016**, *31*, 2665–2667. [CrossRef]
97. Malchau, S.S.; Henningsen, A.A.; Loft, A.; Rasmussen, S.; Forman, J.; Nyboe Andersen, A.; Pinborg, A. The long-term prognosis for live birth in couples initiating fertility treatments. *Hum. Reprod.* **2017**, *32*, 1439–1449. [CrossRef]
98. Hendin, B.N.; Falcone, T.; Hallak, J.; Nelson, D.R.; Vemullapalli, S.; Goldberg, J.; Thomas, A.J.; Agarwal, A. The Effect of Patient and Semen Characteristics on Live Birth Rates Following Intrauterine Insemination: A Retrospective Study. *J. Assist. Reprod. Genet.* **2000**, *17*, 245–252. [CrossRef]
99. Erdem, A.; Erdem, M.; Atmaca, S.; Korucuoglu, U.; Karabacak, O. Factors affecting live birth rate in intrauterine insemination cycles with recombinant gonadotrophin stimulation. *Reprod. Biomed. Online* **2008**, *17*, 199–206. [CrossRef]
100. Ohannessian, A.; Loundou, A.; Gnisci, A.; Paulmyer-Lacroix, O.; Perrin, J.; Courbiere, B. Unexplained infertility: Live-birth's prognostic factors to determine the ART management. *Minerva Ginecol.* **2017**, *69*, 526–532. [PubMed]
101. Reindollar, R.H.; Regan, M.M.; Neumann, P.J.; Levine, B.S.; Thornton, K.L.; Alper, M.M.; Goldman, M.B. A randomized clinical trial to evaluate optimal treatment for unexplained infertility: The fast track and standard treatment (FASTT) trial. *Fertil. Steril.* **2010**, *94*, 888–899. [CrossRef] [PubMed]
102. Thoma, M.E.; McLain, A.C.; Louis, J.F.; King, R.B.; Trumble, A.C.; Sundaram, R.; Buck Louis, G.M. Prevalence of infertility in the United States as estimated by the current duration approach and a traditional constructed approach. *Fertil. Steril.* **2013**, *99*, 1324–1331.e1. [CrossRef] [PubMed]

103. McLernon, D.J.; Maheshwari, A.; Lee, A.J.; Bhattacharya, S. Cumulative live birth rates after one or more complete cycles of IVF: A population-based study of linked cycle data from 178 898 women. *Hum. Reprod.* **2016**, *31*, 572–581. [CrossRef] [PubMed]
104. Smith, A.; Tilling, K.; Nelson, S.M.; Lawlor, D.A. Live-Birth Rate Associated With Repeat In Vitro Fertilization Treatment Cycles. *JAMA* **2015**, *314*, 2654–2662. [CrossRef]
105. Malizia, B.A.; Hacker, M.R.; Penzias, A.S. Cumulative Live-Birth Rates after In Vitro Fertilization. *N. Engl. J. Med.* **2009**, *360*, 236–243. [CrossRef]
106. Chambers, G.M.; Paul, R.C.; Harris, K.; Fitzgerald, O.; Boothroyd, C.V.; Rombauts, L.; Chapman, M.G.; Jorm, L. Assisted reproductive technology in Australia and New Zealand: Cumulative live birth rates as measures of success. *Med. J. Aust.* **2017**, *207*, 114–118. [CrossRef]
107. Yeh, J.S.; Steward, R.G.; Dude, A.M.; Shah, A.A.; Goldfarb, J.M.; Muasher, S.J. Pregnancy rates in donor oocyte cycles compared to similar autologous in vitro fertilization cycles: An analysis of 26,457 fresh cycles from the Society for Assisted Reproductive Technology. *Fertil. Steril.* **2014**, *102*, 399–404. [CrossRef]
108. Baudin, T.; De La Croix, D.; Gobbi, P.E. Fertility and childlessness in the United States. *Am. Econ. Rev.* **2015**, *105*, 1852–1882. [CrossRef]
109. Collins, J. Cost-effectiveness of in vitro fertilization. *Semin. Reprod. Med.* **2001**, *19*, 279–289. [CrossRef]
110. Chambers, G.M.; Sullivan, E.A.; Ishihara, O.; Chapman, M.G.; Adamson, G.D. The economic impact of assisted reproductive technology: A review of selected developed countries. *Fertil. Steril.* **2009**, *91*, 2281–2294. [CrossRef] [PubMed]
111. Katz, P.; Showstack, J.; Smith, J.F.; Nachtigall, R.D.; Millstein, S.G.; Wing, H.; Eisenberg, M.L.; Pasch, L.A.; Croughan, M.S.; Adler, N. Costs of infertility treatment: Results from an 18-month prospective cohort study. *Fertil. Steril.* **2011**, *95*, 915–921. [CrossRef] [PubMed]
112. Gameiro, S.; Boivin, J.; Peronace, L.; Verhaak, C.M. Why do patients discontinue fertility treatment? A systematic review of reasons and predictors of discontinuation in fertility treatment. *Hum. Reprod. Update* **2012**, *18*, 652–669. [CrossRef] [PubMed]
113. Domar, A.D.; Smith, K.; Conboy, L.; Iannone, M.; Alper, M. A prospective investigation into the reasons why insured United States patients drop out of in vitro fertilization treatment. *Fertil. Steril.* **2010**, *94*, 1457–1459. [CrossRef] [PubMed]
114. Perkins, K.M.; Boulet, S.L.; Jamieson, D.J.; Kissin, D.M. Trends and outcomes of gestational surrogacy in the United States. *Fertil. Steril.* **2016**, *106*, 435–442.e2. [CrossRef] [PubMed]