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The NEW ENGLAND JOURNAL of MEDICINE

April 24, 2025

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Sincerely,

Eric J. Rubin, MD, PhD



Hospital-at-Home Practice Emerging as a Growing Venue for Physician Practice

As the nascent model becomes more entrenched, physicians are playing key roles and appreciating the experience

By Bonnie Darves, a freelance health care writer

Physicians who are eager to expand their practice horizon and are interested in using innovative technologies to deliver comprehensive virtual care beyond the video sessions that proliferated during the pandemic may find a good fit in the emerging hospital-at-home programs that health systems are implementing. Physicians who have at least a few years of hospital-based practice experience are being tapped to serve as chief care facilitators or medical directors for hospital-at-home programs, and the demand for such expertise is predicted to grow in the coming years.

Hospital-at-home programs enable patients to receive high-acuity care in their homes, with the clinical oversight of physicians, typically hospitalists, and a combination of remote and onsite care providers. Most models operate from command centers and feature a robust equipment and technological backbone for vitals monitoring and patient communication. In an ideal scenario, hospital-at-home care is intended for patients who are sick enough to warrant hospitalization but stable enough to be safely cared for at home.





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Primary candidates include patients with chronic-condition exacerbations or infections, those undergoing cancer treatment, and immune-compromised individuals at high risk for contracting infections. Some hospital systems are also exploring using the model for post-surgical patients. In many current models, patients who present to the emergency department or are already on medical-surgical units are evaluated by physicians for their potential to be safely treated at home instead of admitted to the hospital.

Hospital-at-home programs are not new. In Canada, England, Australia, and many European countries, such care models are well established, in part because they're easier to implement with single-payer models. In the United States, hospital-at-home programs were relatively rare until the COVID-19 pandemic push came to shove - catalyzing virtual care implementation in 2020 and spurring hospitals to create new programs on the fly.

Johns Hopkins pioneered the hospital-at-home model in the mid-1990s, but a movement didn't ensue. Most of the programs in place today are nascent. However, as the US Centers for Medicare & Medicaid Services continues to grant approval for hospital-at-home programs that meet its criteria — as of June 2024, 331 hospitals in 37 states had been authorized to provide such services, according to the American Hospital Association (AHA) — the model is expected to become more prevalent. AHA, which has 5,000 members, reports growing interest among members in establishing hospital-at-home programs.

The recently formed Hospital at Home Users Group has more than 100 active members, and an additional affiliate group includes hospitals and health systems that are considering establishing programs. These developments will increase demand for physicians, primarily hospitalists, who can help launch and direct hospital-at-home programs.

What hospital-at-home looks like on the ground

Not surprisingly, the hospital-at-home programs that are moving to full implementation are being led by large health systems and commandeered by hospital-based physicians. At Mayo Clinic in Florida, a program initially developed as a response to strained hospital capacity during the pandemic is now a full-scale Advanced Care at Home program. It is staffed by 12 physicians who practice within Mayo's command center and direct care

for patients admitted through multiple Mayo hospitals in Florida, Arizona, and Wisconsin.

"What we've created is essentially an ecosystem that enables us to deliver hospital-level care at home, providing most of the services that eligible patients would receive in the hospital."

- Michael Maniaci, MD, Mayo Clinic

Dr. Maniaci notes that approximately 70 percent of patients who go to the hospital through the emergency department are treated and released; those who would benefit from continued clinical oversight are ideal candidates for hospital-at-home care. Other patients are admitted via hospitals' medical-surgical units.

In the Mayo model, started in 2020 to address the capacity-shortage issues the pandemic created, physicians rotate through the command center on a periodic basis. They work in tandem with nurses and advanced practice providers (APPs) and orchestrate the provision of services ranging from lab tests, imaging, and IV therapies to physical therapy and wound care, among others. Patients are equipped with computers and monitoring devices and a phone line that connects them directly to clinicians at the command center. As in inpatient models, the care team conducts rounds and loops in specialists as warranted. APPs, nurses, and paramedics, Dr. Maniaci explained, are the "boots on the ground."

Laila Hakam, MD, a hospitalist and senior associate consultant at Mayo who helped establish the program and now devotes approximately twothirds of her practice to hospital-at-home care, quickly became enamored of the model. "It's actually become another admitting arm for us, and we're finding that it retains a superior standard of care," Dr. Hakam said. "It's proving a very collaborative approach, and we [physicians] find it's helpful that our virtual nurses are literally just a tap away." Dr. Hakam and her colleagues appreciate the fact that the model gives them a view into home and the supports a patient has — or lacks. "It's contextual medicine practice, and I feel that I'm more available to my patients," she said.

To date, more than 2,000 Mayo patients have been cared for in the hospitalat-home program, and volumes will increase as Mayo expands its program to incorporate a new STAT home-care program and other offerings.

Care models stress multidisciplinary, integrated approach

North Carolina-based Atrium Health, a large integrated system with 68 hospitals across four states, has been a forerunner in positioning physicians at the frontline of virtual, comprehensive home-based care. The program was established rapidly during the pandemic to accommodate urgent overcapacity issues and deliver care to COVID-19 patients. It has since evolved into a sophisticated permanent program that, to date, has treated more than 12,000 patients.

Today, a core group of eight full-time equivalent (FTE) hospitalists and the program's medical director work in tandem with APPs to oversee care in Atrium's Hospital at Home program. An additional 40 hospitalists have been trained and now rotate into the program as moonlighters on an asneeded or as-wanted basis.

Daniel Davis, MD, Atrium's senior medical director of continuing health, expects that number to expand rapidly in the next few years as the health system expands its patient capacity. It permits them to combine "brickand-mortar" practice with virtual care — and develop a new skill set in the process. "It's been a great option for our physicians who have been working in the hospital for ten to 20 years."

"This is definitely an emerging practice area for physicians, and we're seeing a growing number of physicians who are interested in this hybrid practice model."

— Daniel Davis, MD, Atrium Health

In Atrium's model, physicians and nurses work from home rather than from a site-based hub, and clinicians engage in formal multidisciplinary teams. The team includes a "quarterback" physician who assesses referrals and oversees clinical operations. On a given day, a patient might receive imaging, infusion, and therapy services, and Atrium also provides meals when needed. Physicians "see" their patients at least once daily. Those video visits frequently incorporate virtual nurses, onsite paramedics, and family members in the same visit.

Dr. Davis acknowledges that, for physicians, there is a definite learning curve in adapting to the virtual care model and its team structure. "Taking a patient history via video can be challenging at first because it's a different skill set. Physicians also must be very intentional about building relationships with other team members — and trusting them," Dr. Davis said.

Cleveland Clinic, a recent entrant, launched its Hospital Care at Home program in April 2023. Like Mayo, it utilizes a command-center hub, called the Clinically Integrated Virtual Care (CIViC) Center, as its base of operations. Two hospitalists conduct patient rounds and intakes, and five nurse managers provide active oversight and ensure that all services are delivered according to protocol. That physician team is likely to grow soon as Cleveland Clinic expands the model to encompass additional hospitals.

"We're seeing a lot of interest among physicians and nurses who want to join the program," said Richard Rothman, MD, chief of medical operations for Cleveland Clinic in Florida. "In hospital medicine in general, there is a general perspective among physicians that the way we deliver care today isn't the way we'll deliver it tomorrow. We're learning as we go."

What's in it for physicians?

Even though it's early days, Mayo, Atrium Health, and Cleveland Clinic are receiving positive reviews from physicians practicing in their hospital-athome care models. "Our hospitalists are seeing the value of the program for both patients and physicians," Dr. Rothman said. "The hospitalists find that they're having more direct interaction with their patients than they might in the inpatient setting, and that it's easier to incorporate families in discussions about care using the video model."

"In hospital medicine in general, there's a general perspective among physicians that the way we deliver care today isn't the way we'll deliver it tomorrow. We're learning as we go."

- Richard Rothman, MD, Cleveland Clinic

Although there is no formal supporting data to date, Dr. Rothman is optimistic and hopeful that providing hospitalists with care-setting alternatives via the hybrid care model may help reduce the burnout with which many physicians struggle today.

From a career-option standpoint, hospital-at-home practice is best suited to physicians who have at least three to five years of hospital-based practice experience. That is important, all sources concurred, because physicians

must first be deeply familiar with hospital care systems before they attempt to safely replicate comprehensive care in the home setting. "Physicians probably need three to five years of experience in brick-and-mortar work before they transition to a virtual model," said Dr. Davis. "They have to learn what a sick patient looks like," he said, to determine appropriate care plans and decide when interventions are needed.

Irene Rahman-Garcia, MD, an early-career hospitalist who is helping Cleveland Clinic expand its hospital-at-home program, cites a practice benefit some hospitalists are reporting: improved patient compliance with prescribed treatment and services. "We're seeing that patients seem to be more comfortable and peaceful receiving their care at home, where they can be with their family or caregivers and their pets," she said. "Hospitalists get to witness that transition and see the benefits — that the home environment is better for some patients."

Dr. Maniaci hears a similar story from his hospital-at-home physicians. They report that communicating with patients in their home environment helps physicians get to know their patients better. Physicians also appreciate the technological infrastructure and ability to get orders managed expediently. "Our younger, tech-savvy physicians jumped right in when we started the program," he said, and are excited about the sophistication of the care model.

At Atrium Health, hospitalists have been impressed with the efficiency of hospital-at-home care. Initial skeptics have become converts over time, according to Kara Gallagher, MD, a family physician who has practiced full-time in the program for two years and now trains and mentors newcomers. She noted that many physicians are surprised by the level of care provided in a home setting and how comprehensive it truly is.

"Our hospitalists are impressed with the magnitude and scope of what we can offer patients at home. It's not like babysitting a patient at home — it's comprehensive care, and that surprises the physicians initially."

— Kara Gallagher, MD, Atrium Health

Boston Medical Center, which introduced its hospitalist-staffed hospitalat-home program in April 2024, is already witnessing benefits for its physicians and patients, according to Fitzerald Shepherd, MD, the program's

medical director. "What we're hearing from physicians is that seeing patients in their home setting gives them a new dimension into patient care — seeing what happens when a patient goes home from the hospital and the social issues that may impact care," he said, has proved instructive for our hospitalists," Dr. Shepherd said. "Some of our physicians think that [the care model] will help reduce burnout among doctors and nurses." In addition, because the hospital-at-home physicians are physically colocated with nurses, relationships between the two groups, anecdotally, appear to be strengthening, Dr. Shepherd said.

All the programs featured in this article are seeing good results on the all-important measures of patient safety and how patients fare from an outcomes standpoint. Although data are still being gathered, early experience suggests that emergency department visits and hospital readmissions are down and that relatively stable patients appreciate the option of getting their care at home. Colleen Hole, BSN, MHA, who helped Atrium found its hospital-at-home program, said that the ability to provide patients with a "soft landing" at home has lowered ED visits and readmissions, as well as referrals to skilled nursing facilities. "This model has mitigated a lot of the risk," she said, for suboptimal outcomes, which in turn is a relief to physicians. "The hospital-at-home is now truly part of the care continuum."

One observation made by all the sources interviewed for this article is that patients perceive the hospital-at-home services as more attentive and coordinated care rather than "remote" care. "Patients often say that they feel they spent more time with clinical staff at home than when they were in the hospital," said Dr. Davis, "and our physicians appreciate how holistic the care model is."

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Unusual Parts of Compensation Packages

By Nisha Mehta, MD, a physician leader whose work focuses on physician empowerment, community building, and career longevity in medicine

In speaking to so many about their job offers, I've realized that we're often myopic in terms of what we think can be negotiated when discussing a contract. There are the traditional things everyone asks about — salary, bonus structure, call responsibilities, vacation schedule, and signing bonuses, to name a few. However, when talking to people about what their ideal job looks like, there's often more random things on a wish list. What we fail to realize is that those are all things that can be asked for, but that nobody else would even think to offer them to sweeten the deal.

Some examples of these?

- An early start and end to the day
- Dedicated academic or administrative time
- Unique FTEs such as 0.7 or unique structuring of their FTEs, such as alternating four- and two-day weeks
- · Bonuses for creation of alternative revenue streams for the practice
- Changes in the amount of allotted CME money or money for office furnishings or technology

- The ability to work from home a certain number of days a week (for example, doing telehealth)
- A specified patient population according to their area of academic interest/desired practice panel
- · An increased number of support staff such as scribes or medical assistants
- The speaker system which you will have in your operating room

Some of these may sound silly to you to ask for, but I know of physicians who have asked for and received these things as part of their contract negotiations. Remember, what brings happiness in your day-to-day life as a physician is very individualized, and therefore, asking for those things that will enhance your satisfaction (e.g., career longevity) at that job is not unreasonable.

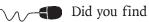
Of course, asking for these things can be an art form. Understand that every institution has different flexibility or bandwidth for accommodating individual requests. You may want to look at what other accommodations have been made for other physicians on staff as precedent for what may be realistic prior to compiling your list of asks. Also, be careful about how many of these additional things you ask for. If you have 10 unusual requests, even if they are relatively minor, the message to the employer could be that this is a pattern of behavior where you will always be asking for exceptions to normal operating procedures.

Figure out which ones mean the most to you. Also figure out which ones are going to be harder to negotiate later, as your negotiating power is always greatest before you sign a contract. Be prepared to justify the asks so they understand why they would make accommodations. For example, if you are able to clearly articulate why something will lead to increased efficiency, lead to better patient outcomes, or contribute to your career longevity and prevent burnout, this would help your case. It would also help them to explain to others who question why these special accommodations were granted.

As demographics in medicine change, unusual asks will become more frequent. The sustainability of our health care workforce requires out-of-thebox solutions, and for some of you, these may be part of them! If you don't ask, you won't get it.

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CLINICAL PRACTICE

Infertility Evaluation and Treatment

Nanette Santoro, M.D.,^{1,2} and Alex J. Polotsky, M.D.^{1,2}

This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.

A couple presents after 1 year without conception despite having had sexual inter- Author affiliations are listed at the end of course 2 or 3 times per week. The 36-year-old female partner has menses (lasting 3 to 5 days) every 26 to 30 days. Neither partner has active medical problems; both are taking vitamins aimed at supporting fertility. They would like to have three children. How would you evaluate and treat this couple?

THE CLINICAL PROBLEM

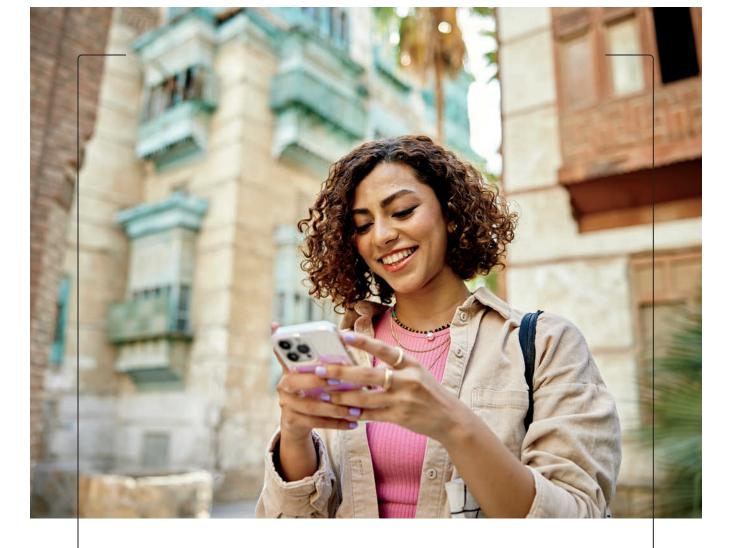
RIMARY INFERTILITY IS DEFINED AS A HISTORY OF NO PREVIOUS CONCEPtion, and secondary infertility is an inability to conceive after any previously documented pregnancy. As defined by the American Society for Reproductive Medicine (ASRM), any need for reproductive technology in order to conceive is meant to be inclusive of same-sex couples, single parents by choice, persons who want to freeze oocytes, and transgender persons.¹

Assisted conception accounts for 5% of U.S. births.² Although in vitro fertilization (IVF) was invented to circumvent blockage of the fallopian tubes, the expected live birth rate with IVF per round of treatment exceeds that of a couple with normal fertility in any given cycle and surpasses all other treatments to obtain a live birth (Table 1). This degree of efficacy has led to the use of IVF for the treatment of infertility due to almost any cause. However, fertility treatment is expensive in the United States, and insurance coverage is inconsistent, factors that lead to inequitable access. Only 21 states mandate partial or complete insurance coverage. Regardless of access, Black, Hispanic, and Asian persons have lower live birth rates than White persons with most treatments, particularly IVF.³

STRATEGIES AND EVIDENCE

HISTORY AND EXAMINATION

A comprehensive evaluation includes a detailed menstrual history and assessment of risks for anatomical infertility, such as previous pelvic surgery or infection. Medications that are potentially hazardous for pregnancy or conception (e.g., retinoids, methotrexate, and lithium) should be reviewed for replacement with appropriate alternatives. A history of testicular injury or undescended testes should be obtained, along with an assessment for androgenic steroid use, which is increasingly common among U.S. men 18 to 45 years of age.⁴ An evaluation should focus on clinical information relevant to common causes of infertility: extremes of weight, signs and symptoms of polycystic ovary syndrome (PCOS; e.g., hirsutism, acanthosis nigricans, and oligomenorrhea), premature ovarian insufficiency (e.g., night sweats), hyperprolactinemia (e.g., galactorrhea), and other possible endocrine



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the article. Dr. Santoro can be contacted at nanette.santoro@cuanschutz.edu or at the University of Colorado School of Medicine, 12631 E. 17th Ave., Aurora, CO 80045.

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KEY POINTS

INFERTILITY EVALUATION AND TREATMENT

- The age of the childbearing female partner is the most important predictor of live birth with natural conception as well as with assisted conception.
- The probability of live birth with a single cycle of in vitro fertilization therapy exceeds the monthly fecundability of natural conception, thereby leading to its dominant role in fertility treatment.
- At least one third of infertility cases are due to male reproductive issues that could be effectively managed with assisted conception.
- An evaluation should focus on clinical information relevant to common causes of infertility: extremes of weight, signs and symptoms of polycystic ovary syndrome, and other possible endocrine disturbances.

betes, and hypogonadism). A single abnormality, of primordial ovarian follicles.9 Measurement of if found, should not be assumed to wholly ex- the levels of follicle-stimulating hormone (FSH) plain a couple's infertility. Complete testing of and estradiol in the early follicular phase (menboth partners is recommended in most cases. strual cycle days 2 to 4, when FSH is typically at Patients' intentions with regard to their hoped-for its follicular-phase peak) provides indirect inforfamily size and potential consideration of donor mation about ovarian reserve. Because more FSH gametes or embryos can inform longer-term thera- is required to cause follicular maturity as ovarian peutic options.

RECOMMENDED ROUTINE TESTING Semen Analysis

repeated if the results of the first analysis are out- of at least 12, a level of antimüllerian hormone side the normal range.⁵ An abnormal semen chargereater than 1 ng per milliliter, an FSH level of acteristic (e.g., low sperm concentration, sperm less than 10 IU per liter, and an estradiol level of dysmotility, or abnormal morphologic features) is less than 80 pg per milliliter. Decreased ovarian detected in approximately one third of couples reserve is observed in approximately 26% of pawith infertility (Table 1). In cases of a varicocele, tients presenting to IVF centers in the United fertilization failure, poor embryo development af- States.¹⁰ Patients with decreased ovarian reserve ter IVF, or recurrent pregnancy loss, an assess- are usually directed toward more aggressive treatment of sperm DNA fragmentation may inform ment because the course of progression to ovari-

Ovarian-Reserve Testing

The age of the childbearing female partner is the milliliter¹¹) or antral follicle counts (greater than most important predictor of live birth, regardless 25¹²) indicate the presence of PCOS and predict of ovarian reserve.⁷ However, evaluation of ovar- a strong response to ovarian stimulation. ian reserve should be undertaken regardless of age. A combination of ultrasonography and serum Ovulatory Evaluation markers assess both visible and implied numbers Release of a viable egg is mandatory for concepof ovarian follicles as well as the likely response tion. Women reporting monthly menses every to gonadotropins. The number of all follicles 2 mm 28 days are presumed to be ovulatory, and routo 10 mm in diameter (measured with the use of tine confirmation of ovulation is not necessary.¹³ ultrasonography) in both ovaries determines the Premenstrual symptoms such as breast tenderantral follicle count.⁸ Antimüllerian hormone, ness and abdominal bloating are supportive of which is not dependent on the stage of the men- ovulation. Home urine testing for the midcycle strual cycle, is produced by the granulosa cells of luteinizing hormone (LH) surge is widely available, early-developing follicles and is the most direct and a positive surge result approximately 14 days

disturbances (e.g., hypothyroidism, type 2 dia- serum biomarker that quantifies the relative pool reserves dwindle, the follicular phase shortens with earlier elevation of estradiol. Therefore, elevated levels of FSH and estradiol indicate decreased ovarian reserve. Adequate ovarian reserve Semen analysis is recommended and should be thresholds are shown by an antral follicle count a recommendation for the use of donor gametes.⁶ an failure in such patients is unpredictable and may be rapid. Very high levels of antimüllerian hormone (greater than approximately 6 ng per

Table 1. Infertility Causes, Prevalence, and Management Approaches.*

	Cause	Prevalence	Treatm
		%	
ĺ	Ovulatory dysfunction	25 ¹⁵ †	Induction of
	Polycystic ovarian syndrome	8–13 ¹⁹ ‡	Letrozole ²¹ cycles, Clomiphen cycles,
	Functional hypothalamic amenorrhea	1 ²⁵ ‡	Cognitive b Clomiphen Gonadotro
	Premature ovarian insufficiency	1 ²⁶ ‡	Oocyte dor
	Diminished ovarian reserve ¹⁰	19–26 ¹⁰ †	IVF (live bi
	Uterine factor	2–17 ³³ †	Individualiz
	Fallopian tube patency ³⁰ ¶	11–67 ⁴⁶ †	IVF (live bi Hydrosalpi pregnai
	Endometriosis	25–50 ³⁴	IVF (live bi
	Abnormal semen characteristics	5-4015	IUI (NA) IVF (live bi
	Unexplained infertility**	15	IUI with clo IUI with let IUI with go for up t IVF (live bin

* Live birth rate is reported by the Society for Assisted Reproductive Technology as live births per initiated stimulation cycle in women younger than 35 years of age or for all donor oocyte cycles initiated.³⁸ IUI denotes intrauterine insemination, IVF in vitro fertilization, and NA insufficient data to report outcomes.

- Shown is the prevalence among couples with infertility.
- Shown is the population prevalence of the disorder.
- Clomiphene may be considered for treatment in women with functional hypothalamic amenorrhea if the patient's initial estradiol level does not indicate complete suppression of the hypothalamic pituitary axis.
- Prevalence varies widely depending on the population

The prevalence of endometriosis among adults in the U.S. population is 10 to 15%.³⁴ 🗱 Multiple gestation occurred in 13% of gestations with letrozole, 9% with clomiphene, and 32% with gonadotropin. There were 10 triplet gestations, all in patients who were treated with gonadotropin

menses, infrequent menses, or inadequate pro- ian insufficiency). gesterone production indicate oligo-ovulation or anovulation. Testing for hyperprolactinemia, PCOS Evaluation of the Fallopian Tubes and Uterus

before menses is confirmatory, as is a midluteal (7 PCOS, psychosocial assessment for women with days before expected menses) serum progesterone hypothalamic amenorrhea, and genetic and autolevel of 3 ng per milliliter or higher.¹⁴ Absence of immune workups for women with premature ovar-

(levels of androgens and 17-hydroxyprogesterone Anatomical abnormalities (e.g., fallopian tube ocand the LH:FSH ratio), congenital adrenal hyper- clusion, pelvic adhesions, and other tubal abnorplasia (level of 17 hydroxyprogesterone), hypogo- malities) accounted for up to 34% of infertility nadotropic amenorrhea (levels of LH, FSH, and factors in women in one large World Health Orestradiol), or premature ovarian insufficiency ganization study of 8500 couples with infertility.¹⁵ (levels of FSH and estradiol) are indicated de- Hysterosalpingography and sonohysterography with pending on the clinical presentation. Further test- or without a saline-air device are noninvasive teching specific to each condition may also be indi- niques that have largely supplanted laparoscopy cated (e.g., metabolic assessment for women with to determine tubal patency as well as intrauterine

ment Option (Reported Outcome per Treatment Cycle) of ovulation (live birth, 35.4%)³⁸ ¹ (live birth, cumulative for up to five 27 5%) ne (live birth, cumulative for up to five , 19.1%) behavioral therapy²⁴ (NA) ne (NA)∬ opin (NÅ) onation (live birth, 39.0%)³⁸ birth, 19.9%)38 ized (NA) oirth, 38.1%)30,38 pinx removal³⁰ (odds ratio for clinical ancy, 4.66; 95% CI, 2.47 to 10.01) pirth. 39.5%)38 oirth, 40.8%)38 lomiphene³⁶ (live birth, 23.3%) etrozole³⁶ (live birth, 18.7%) onadotropin³⁶ (live birth, cumulative to four cycles, 32.2%)

birth, 39.9%)38

involve retrograde instillation of either radiologic (with 62% vs. 45% of treatment cycles leading to contrast (hysterosalpingography) or saline and ovulation).²⁰ Letrozole was more effective than air (ultrasonography-based methods) to separate clomiphene for ovulation induction and live birth the uterine walls and push fluid through the fal- in women with PCOS (Table 1).²¹ Although helplopian tubes, which allows visualization of the ful for preventing type 2 diabetes, metformin led uterine cavity and tubal patency.

TREATMENT

TREATMENT OF INFERTILITY ATTRIBUTABLE TO THE MALE PARTNER

have been suggested to improve semen quality; of 13 randomized clinical trials involving 1132 however, none, including vitamins, have sufficient persons did not show a benefit in live births evidence to warrant their use.¹⁷ With regard to with concurrent metformin treatment during an varicoceles, no clinical trial evidence has shown IVF cycle.²³ that surgical treatment improves fertility.

mechanical manipulation of semen by means of amenorrhea (in 1% of women with amenorsuspending a sperm concentrate in culture medi- rhea^{24,25}), premature ovarian insufficiency (in $1\%^{26}$). um and injecting it into the uterine fundus at the and prolactinoma (in $0.3\%^{27}$). Management of hytime of ovulation (intrauterine insemination [IUI]), pothalamic amenorrhea includes cognitive behavplacing sperm directly onto oocytes in vitro, or ioral therapy to help address causal stressors such mobilizing a single sperm cell and injecting it as low body weight or low body fat, psychogenic directly into an oocyte during IVF (intracytoplas- stress, negative energy balance, and excess exermic sperm injection).

mally low motile sperm counts are candidates for mal ranges when ovulatory function is reestab-IUI. For motile sperm counts below the range of lished.²⁴ Premature ovarian insufficiency is not re-1 million to 5 million, IVF with direct sperm injec-versible; when prolonged amenorrhea is observed, tion is the treatment of choice. Despite increased pregnancy is unlikely, regardless of treatment. use of this technique to ensure against fertiliza- Prolactinomas in women are usually responsive tion failure, a cohort study of more than 300,000 to medical management with dopamine agonists IVF cycles showed lower rates of implantation and (cabergoline or bromocriptine); live birth rates as live birth when intracytoplasmic sperm injection high as 94% have been reported once prolactin was performed for indications other than severe levels normalize.²⁸ male infertility.18

TREATMENT OF OVULATORY DISORDERS

Although IVF is the most successful treatment need IVF therapy to conceive. If a hydrosalpinx option for almost all ovulatory disorders, whether is present, removal or complete occlusion of the to try ovulation induction or stimulation strate- affected tube, treatment with antibiotic agents, gies first merits consideration because of the or aspiration is recommended. Findings from associated cost and invasiveness of IVF (Table 1). retrospective studies and limited data from ran-PCOS, the most common endocrinopathy in wom- domized clinical trials support this practice. In en, affects 6 to 13% of women of reproductive one study involving 192 women, live births ocage worldwide.¹⁹ A secondary analysis of ran- curred in 28.6% of the women who were randomized trials involving women with PCOS and domly assigned to undergo hydrosalpinx removal, obesity showed that deferred ovulation induc- as compared with 16.3% (P=0.045) of the women tion preceded by lifestyle interventions and hor- who received no intervention.²⁹ A Cochrane Review monal contraception resulted in significantly more reported data from five clinical trials involving

fibroids, polyps, and adhesions.¹⁶ Both methods ovulation than immediate ovulation induction to fewer 6-month cumulative live births (in 7.2% of the women who received it) than clomiphene (in 22.7%) in a large, U.S. network-based clinical trial.²² IVF is a favorable second-line option for women with PCOS, because their increased number of ovarian follicles usually leads to highly A variety of products (devices and supplements) productive egg harvesting. A Cochrane Review

Other common ovulatory disorders that cause Most treatments of male infertility involve the amenorrhea include functional hypothalamic cise. Gonadotropin injections can also be used to Couples in which the male partner has abnor- induce ovulation. Pregnancy rates approach nor-

TREATMENT OF TUBAL AND UTERINE FACTORS

Women with fallopian tube occlusion or removal

removal has been questioned.

tum surface constitutes a poor implantation site. trial of clomiphene did not result in a live birth.³⁷ However, a randomized, international, multicenter clinical trial that compared septum removal with IN VITRO FERTILIZATION tion.33

TREATMENT OF ENDOMETRIOSIS

that of unexplained infertility.³⁵

TREATMENT OF UNEXPLAINED INFERTILITY

626 women that supported the benefit of hydro- Clomiphene is the treatment of choice on the salpinx removal on pregnancy rates, but the re- basis of a multicenter clinical trial evaluating the port noted that the trials produced limited data use of clomiphene, letrozole, or gonadotropins with regard to live births and the value of drain- along with IUI in 900 couples with unexplained age or occlusion.³⁰ Given the effectiveness of IVF infertility (Table 1). The higher live birth rate with in producing live births, the need for hydrosalpinx gonadotropin–IUI treatment in this trial was offset by its unacceptably high incidence of multi-Among uterine disorders, septa (estimated prev- ple pregnancy (32% of pregnancies) as compared alence, 0.2 to 2.3%) are often found during the with clomiphene (13%) and letrozole (9%).³⁶ A fertility workup. Septum excision has been recom- separate randomized trial evaluating time to mended in patients with a history of pregnancy pregnancy and overall cost found no benefit of loss, in the belief that the relatively avascular sep- performing gonadotropin-IUI before IVF if a

expectant management in women with previous In 1978, the year of the first live birth of a baby pregnancy loss showed no benefit with septum conceived through the use of IVF, the probabilresection.³¹ Other uterine causes of infertility, such ity of a successful live birth as a result of IVF was as fibroids and synechiae, are managed on the less than 10%. In 2021, women younger than 35 basis of the signs and symptoms specific to the years of age had a 43.1% probability of live birth patient. Surgical management of asymptomatic from a single IVF attempt (Table 1)³⁸; outcomes fibroids remains controversial, and treatment is were worse with increasing age (31.0% for womcurrently individualized.³² Uterine lesions are typ- en 35 to 37 years of age, 19.0% for those 38 to 40 ically treated with outpatient hysteroscopic resec- years of age, 9.4% for those 41 to 42 years of age, and 3.2% for those older than 42 years of age).

The process of an IVF cycle is shown in Figure 1. Exogenous gonadotropin stimulation is Although the estimated prevalence of endome- combined with suppression of the hypothalamictriosis is 2 to 10% among all women, it is found pituitary axis with a gonadotropin-releasing horin 25 to 50% of women with infertility.³⁴ When mone (GnRH) antagonist or, less frequently, an endometriosis is diagnosed, surgical excision or agonist to prevent an endogenous LH surge and fulguration, followed by expectant management, override the body's natural system of avoiding is preferred.³⁵ However, since routine laparosco- multiple folliculogenesis. After stimulation for py is no longer part of the infertility workup, approximately 10 days, the final stages of oocyte occult endometriosis may be present. Because of maturation are initiated with human chorionic the invasive and inflammatory nature of ovarian gonadotropin (HCG) or an GnRH agonist (or endometriosis, this disorder can reduce ovarian both), with the latter used to provide a shorterreserve and cause pelvic adhesions and tubal oc- acting burst of endogenous LH. Before oocytes clusions that further compromise fertility. IVF is are extruded, they are retrieved by means of often the preferred treatment to hasten time to needle aspiration guided by transvaginal ultrapregnancy in women with severe endometriosis. sonography and inseminated either by overlay-However, in mild disease in which cytoreductive ing of concentrated sperm or by direct oocyte surgery has been performed and symptoms have injection. Fertilized oocytes are grown in vitro not recurred, management is more consistent with for 5 days, by which time they have reached the blastocyst stage and are ready for uterine transfer. Embryo transfer can be performed at this time, but concern about supraphysiologic hor-By definition, unexplained infertility is present mone exposure of the uterus has led to embryo when a complete workup fails to yield a cause. A transfers more commonly being performed after stepwise approach to treatment, beginning with cryopreservation and thawing of the embryo. mild ovarian stimulation combined with IUI, Cryopreservation and thawing allows the female is typically performed for up to 4 to 6 cycles. partner time to recover from the oocyte retrieval

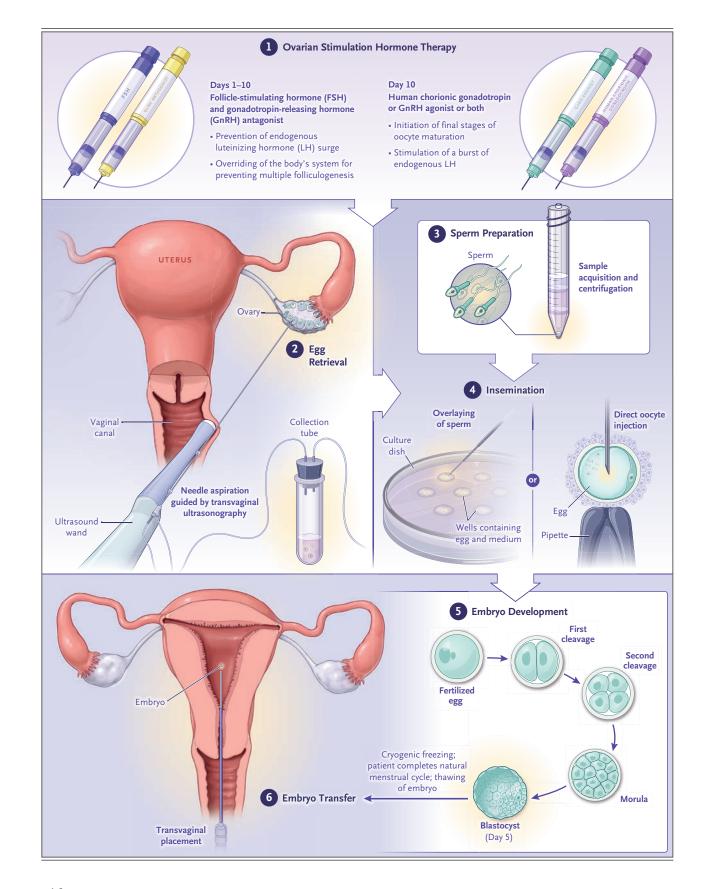


Figure 1 (facing page). Process of IVF.

women with regular menses.⁴¹ Our recommendations align with those of ASRM.

AREAS OF UNCERTAINTY

procedure and to undergo either a natural menstrual cycle, wherein the embryo is implanted after More evidence is needed with regard to the effects ovulation occurs spontaneously, or a programmed on fertility of endocrine-disrupting chemicals. The cycle, in which the uterus is primed with exogenous estradiol and progesterone before embryo practice remains a subject of debate.⁴² Although transfer.

Risks associated with IVF include ovarian hy- risks the discarding of embryos that might otherperstimulation syndrome and multiple births. wise be viable; because euploid cells develop more Ovarian hyperstimulation syndrome occurs with rapidly than aneuploid cells, embryos with aneuprolonged exposure to LH or HCG in susceptible ploid cell lines may outgrow the aneuploidy.⁴³ persons when estradiol levels are extremely high. It can largely be avoided by adjusting the gonado- cycle embryo transfer as compared with an artropin dose, cancelling and restarting the cycle at tificial cycle in which exogenous estrogen is a lower dose if the response is too great, avoiding provided in physiologic amounts is of interest, a "fresh" embryo transfer (rather than a transfer because the risk of hypertensive disorders of of the embryo after cryopreservation and thaw- pregnancy may be increased in the absence of ing) if the estradiol level is too high, using lower a corpus luteum.⁴⁴ Finally, premature ovarian indoses of HCG to complete follicle maturation, sufficiency and its precursor, decreased ovarian and triggering final follicle maturation with a reserve, remain a barrier to pregnancy that is GnRH agonist to induce a burst of LH, which difficult to overcome with the use of current methhas a shorter half-life than HCG. Complications ods. The effects of supplying growth factors or related to egg harvesting are rare (occurring in stem cells to ovaries with limited remaining fol-1 in 1000 procedures) and include bleeding or licles are areas of active investigation.⁴⁵ trauma to the ovary or adjacent organs (or both) due to misplacement of the needle.

Multiple births resulting from IVF, an early concern with the technology, have decreased dramatically with the ability to grow embryos in Regarding the couple described in the vignette, 4% and almost no triplet pregnancies.³⁸

GUIDELINES

Embryology (ESHRE), among others, address family size. the various types of infertility.³⁹ Some notable differences exist that may reflect regional policy considerations. For example, ASRM recommends routine initial testing for ovarian reserve,⁴⁰ but ¹Department of Obstetrics and Gynecology, University of Colo-

vitro for 5 to 7 days. By this stage of develop- the negative evaluation is diagnostic of unexment, embryo viability is so robust that transfer plained infertility. Because they hope to have of a single embryo results in excellent live birth three children, we recommended IVF with storrates. In 2022, a total of 73.9% of all IVF cycles age of cryopreserved embryos for future use. reported to the Society for Assisted Reproductive Their IVF procedure resulted in 13 oocytes, 9 of Technology involved the transfer of a single em- which were fertilized and 6 of which became bryo, with an overall multiple pregnancy rate of healthy blastocysts. One blastocyst was implanted during an IVF cycle, and a baby boy was born. We advised the couple to return 18 months after their son's birth to plan for implantation of one of the 5 remaining cryopreserved embryos. Their Practice guidelines published by ASRM and the excellent yield of high-quality embryos makes it European Society for Human Reproduction and likely that this couple will achieve their desired

the full text of this article at NEJM.org.

AUTHOR INFORMATION ESHRE does not recommend this approach in rado, Aurora, CO;²Shady Grove Fertility, Greenwood Village, CO.

role of preimplantation genetic testing in IVF this testing may reduce the time to live birth, it

The value of performing a fresh or natural

CONCLUSIONS AND RECOMMENDATIONS

Disclosure forms provided by the authors are available with

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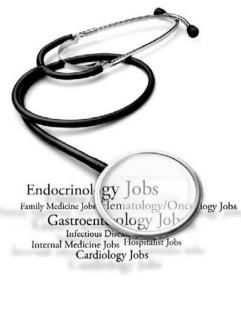
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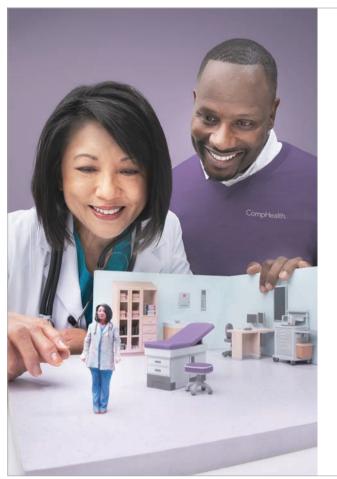
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