ORIGINAL RESEARCH

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Restorative reproductive medicine (RRM) outcomes compared to in-vitro fertilization (IVF) for the treatment of infertility: a retrospective evaluation of a 2019 clinic cohort compared to one cycle of IVF

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ABSTRACT

Objectives: Restorative Reproductive Medicine (RRM) is an emerging approach that can be used to treat infertility. Our goal was to compare RRM to IVF outcomes in 2019.

Methods: We conducted a retrospective clinic-based analysis and referenced it against publicly available data from IVF registries, as published by the Centers for Disease Control and Prevention (CDC) or the Society for Assisted Reproductive Technology (SART) in the USA, and the Human Fertilization and Embryology Authority (HFEA), in the UK. Data from 2019 was collected from routine medical records following treatment at one clinic in Dublin, Ireland during 2019. We defined the demographics, diagnoses, and treatments and then calculated the crude percentages of conception, live birth, multiple pregnancy, prematurity, and low birth weight. These results were benchmarked against data reported in IVF databases.

Results: 249 couples had at least one RRM consultation, 187 committed to the RRM treatment program and met the inclusion criteria. The average female age for all included patients was 36.4 years and couples were trying to conceive for a mean of 32.2 months. Of the 187 patients/couples who underwent treatment, 28% had a previous live birth, 30% had a previous miscarriage, and 42% had never conceived;19% (35/187) had previously had IVF, 2.3 $\pm$ 1.6 IVF cycles per couple. Of the 187 couples, 52% (98/187) conceived, 41% (77/187) had a documented live birth. There were 75 singletons and 2 sets of twins, producing 79 babies. Time to conception for live birth patients averaged 12 $\pm$ 8 months. The average birth weight was 3422g (7lb 9oz) and average weeks' gestation at delivery was 39 $\pm$ 1.5 weeks. 4.0% (3/75) of singleton babies were premature (33-37 weeks) and none were very premature ($\leq$ 32 weeks). 5.3% (4/75) of singleton babies had low birth weight (< 2,500g). When we compared births across age groups, the RRM percentages with live birth were comparable to those in a single cycle of IVF with multiple subsequent embryo transfers, and greater than a single cycle of IVF with a single embryo transfer. Furthermore, RRM babies had fewer multiple pregnancies, and singleton RRM pregnancies had less than half as many premature deliveries compared to IVF, (6.5% RRM all pregnancies or 4.0% RRM, singleton pregnancies vs 14.4% SART, all pregnancies or 11.8% CDC, singleton pregnancies). 74% (26/35) of couples who remained in contact with us and tried for another pregnancy had a repeat successful live birth.

Conclusions: In our clinic, a comprehensive RRM assessment and treatment followed by up to 12 optimal cycles of timed intercourse resulted in a 41% live birth rate (crude rate). We propose that using RRM may improve a couple's chance of having a healthy pregnancy and reduce the demand for IVF. Furthermore, RRM reduces the risk of multiple pregnancy, low birth weight and premature delivery compared to IVF. The majority of couples who sought a second live birth were successful.

Limitations and future directions: This is a retrospective analysis with a small number of RRM patients, compared to large IVF databases of patients using one cycle of IVF, including all transfers made from the IVF retrieval. While useful for benchmarking, conclusions are limited by sample size, and the lack of relevant prognostic data (other than female age) for the IVF patients. Larger prospective studies with full prognostic data are needed to make a proper comparison of RRM and IVF outcomes.

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INTRODUCTION

Infertility is defined as the failure to conceive after 12 months of non-contraceptive intercourse. Restorative Reproductive Medicine (RRM)[1] is a re-emerging medical approach to infertility that seeks to improve diagnosis and treatment based on natural functions of the reproductive system. Medically, the symptom of infertility is like a chronic illness that is caused by multiple factors and often worsens over time.[2] RRM considers infertility as part of a spectrum of impaired reproductive function that includes a delay in conceiving, increased risk of miscarriage, ectopic pregnancy, premature delivery, pregnancy complications and poor perinatal health.

RRM is based on the conviction that healthy women and men have the best chance of being fertile and that impaired fertility indicates the presence of one more underlying diseases or disorders. Researchers published a finding in 2021 regarding male fertility,[3] that men with impaired fertility live sicker and die younger, they have a higher incidence of cardiovascular disease, hospitalization, diabetes, and autoimmune illness. Other data demonstrates the same risks apply to women with infertility.[4] The goal with RRM is to find and treat underlying factors that are contributing to the symptom of infertility. Prior to the development of IVF, restorative evaluations and treatments were common, but having IVF available may have reduced the development and use of restorative or natural approaches.

It is currently unproven if a more persistent restorative approach can be as effective as IVF for overcoming infertility in a general population. There has never been a direct comparison, and IVF clinicians may be following different guidelines for preliminary work-up prior to IVF, which may miss some diagnoses detected by RRM.

In this paper, we report the pregnancy and live birth results, as well as diagnostic evaluations of RRM treatment by one clinic in Dublin, Ireland, for all infertility patients started in 2019, and compare these to IVF outcomes (single cycle) and diagnostic evaluations also from 2019, published by the Centers for Disease Control and Prevention (CDC),[6] the Human Fertilization and Embryology Authority (HFEA),[7] and the Society for Assisted Reproductive Technology (SART)[8] national registries. These registries capture specific demographic and outcome data where compliance is either mandated (CDC, HFEA) or voluntary (SART). Each database is available to the public on the internet and reports the information slightly differently. It is important to point out that the CDC and SART databases report on a similar patient cohort and are not independent patient groups. Most clinics report to both CDC and SART, but the CDC database is legally required, so about 10-20% more of the US clinics only report to the CDC. Using data reported from all three registries helped us to make more robust comparisons.

METHODS

The RRM approach used at the NeoFertility clinic has been developed over the past 27 years. It includes 3 phases. Phase 1 is finding the underlying causes of infertility, and it lasts about 2 months. Phase 2 is attempting to correct those underlying conditions, and it lasts about 2 months. Phase 3 is attempting natural conception when optimal cycles have been achieved, and it can last for 1-18 months.

The key components of Phase 1 are collecting a thorough medical history and teaching patients how to accurately chart their fertility cycle using the Chart Neo App. Correct charting of the menstrual cycle is vital to determine cycle health and confirmation of the stage of the cycle which is subsequently used for proper blood sampling and medication timing. Chart Neo uses proven fertility biomarkers, especially cervical mucus and basal body temperature, adapted from established fertility awareness-based methods (FABMs) including the Billings Ovulation Method®, the Creighton Model Fertility Care System™, and the Sympto-thermal method.[9] The woman enters daily biomarker observations into the app which can be used prospectively to determine the fertile window (for optimal timing of intercourse) and the phases of the menstrual cycle (to evaluate ovulatory function). Key diagnostic evaluation includes day 3 blood tests, and 7 days post ovulation (7 DPO) levels of estradiol and progesterone. Metabolic assessment is also performed when indicated. Common conditions identified in the female include endometriosis, polycystic ovarian syndrome, sleep apnea, chronic fatigue or stress, depressed mood, premenstrual syndrome, insulin resistance, or auto-immune diseases.

Male fertility is also assessed by semen analysis using current World Health Organisation (WHO) criteria, and sperm deoxyribonucleic (DNA) fragmentation testing. Underlying male health issues are investigated similarly as the female partner.

Interventions during Phase 2 may include diet, supplements and medications appropriate for the conditions identified in Phase 1. Surgical referrals are made as indicated, e.g., for endometriosis or varicocele. Female medications may include dehydroepiandrosterone (DHEA), progesterone, levothyroxine, low-dose naltrexone, metformin, prednisolone, and cycle stimulation drugs such as letrozole, clomiphene, follicle stimulating hormone (FSH) and human chorionic gonadotropin (HCG). These medications are monitored and managed until reproductive hormones are balanced based on 7 DPO levels, follicle rupture is confirmed by ultrasound, and adequate luteal support is achieved.

Phase 3 then begins to guide up to 12 optimal cycles of attempted natural conception by sexual intercourse during the fertile window, informed by using the Chart Neo app. If ovarian stimulation is necessary to achieve optimal ovulation and adequate hormone levels, it is done and monitored closely using the Chart Neo app, monthly blood tests on 7 DPO, and ultrasound. The stimulation drugs are titrated to

achieve follicular recruitment of one mature follicle per cycle, and its release (ovulation).

We collected data retrospectively from the medical records of all couples who attempted RRM treatment from one clinic in Dublin, Ireland during 2019. We divided RRM patients into 4 groups, defined as patient couples who had a live birth, miscarried, failed to conceive or were excluded. We excluded couples who withdrew from evaluation or did not initiate treatment, who had serum FSH>30 mIU/ml (female), or who had total sperm counts below 1 million. We analyzed if the patients who opted out were different than the remaining groups by comparing the patient groups for demographic factors and initial diagnoses (prior to RRM evaluation). Comparisons of diagnoses between the RRM groups were analyzed by Fisher's exact test and demographics by analysis of variance using Stata (Stata Corporation, College Station, TX, USA). We compared diagnoses before RRM evaluation (i.e., from evaluations prior to presenting for RRM) and after RRM evaluation. We calculated frequencies of treatments received before conception and during pregnancy. We calculated the crude percentages of conception, live birth, multiple pregnancy, prematurity, and low birth weight for the cohort of 187 patients.

We compared RRM live births and related outcomes to one cycle of IVF, stratified by female age, with published IVF registry data from the USA (CDC),[6] (SART)[8] and the UK (HFEA),[7] excluding older age groups, which had much smaller numbers for RRM. We compared additional information on live births by diagnosis and pre-term births from one of the registries where this information was accessible (SART), and also compared RRM live birth rates to the live birth rates both single and multiple embryo transfers (from a single retrieval).

RESULTS

For RRM in 2019, 249 couples had an initial RRM consultation. Of these, 62 couples were excluded for the following reasons: quit the program before evaluation or attempting to conceive (n=52), female baseline FSH level>30mIU/mL (n=5), male total sperm count < 1 Million per mL (n=2), or already pregnant before starting treatment (n=3). Combining the elevated female baseline FSH level (n=5) and the severe oligozoospermia (n=2), only 3% of patients were judged not medically eligible for RRM treatment. 187 committed to the RRM treatment program and represents the treatment group. The average female age for the treatment group was 36.4 years and couples on average were trying to conceive for 32.2 months. Average male age was 38.0 years. The demographics reported for the RRM clinic compared to the demographics available in the IVF registries can be found in Table 1. The mean female age was similar for the RRM and all IVF registries which reported it. Other key demographic and clinical characteristics that would impact the likelihood of pregnancy and live birth (such as male age, prior pregnancies, or time trying to conceive) were not reported in the IVF registries.

Table 1. Dublin Clinic restorative reproductive medicine (RRM) and in-vitro fertilization (IVF) registry baseline patient characteristics in 2019.

Dataset	RRM treated	CDC IVF[a]	SART IVF[b]	HFEA IVF[c]
Number of patients or IVF cycle starts	187	330,773	127,175	33,861
Mean age female, years	36.4	36.1	NA	34.9
Mean age male, years	38.0	NA	NA	NA
Mean months trying to conceive before treatment	32.2	NA	NA	NA
Mean number of previous pregnancies	1.4	NA	NA	NA
Previous live birth	28%	NA	NA	NA
Previous miscarriage	30%	NA	NA	NA
Mean number previous ovulation induction cycles	0.3	NA	NA	NA
Percent of patients with previous IVF	19%	NA	NA	NA

IVF registries

[a]*CDC- https://archive.cdc.gov/www_cdc_gov/art/reports/2019/pdf/2019-Report-ART-Fertility-Clinic-National-Summary-h.pdf , page 27, figure 1, average age of patients using ART services. Included patients undergoing fertility preservation*

[b]*SART- https://www.sartcorsonline.com/Csr/Public?ClinicPKID=0, Filter for 2019, Live births per intended egg retrieval (all embryo transfers), patients' own eggs.*

[c]*HFEA- https://www.hfea.gov.uk/about-us/publications/research-and-data/fertility-treatment-2019-trends-and-figures/, download data set, Table 3, Female average patient age, 2019.*

Dublin RRM patient characteristics are reported according to pregnancy outcome, or exclusion from the study, in Table 2. Patients who subsequently had a live birth were younger and were trying to conceive for a shorter period. Patients who miscarried had a higher incidence of previous pregnancies and miscarriages. Patients who failed to conceive had the highest proportion who had previously attempted IVF. The

patients who were excluded (mostly for not continuing in care) were similar to those who continued in treatment.

Table 2. Dublin Clinic RRM 2019 patient characteristics by pregnancy outcome, or exclusion from study.

Patient Outcome	Had Live Birth[a]	Miscarried	Failed to conceive	Excluded or withdrew[b]
Number of patients	79	19	89	62
Mean age female, years[c]	35.2	37.9	37.1	37.4
Mean age male, years	38	37.4	38.8	39.5
Mean months trying to conceive before treatment[c]	24.4	29.4	39.8	34.8
Mean number of previous pregnancies[c]	1.8	3.2	0.6	1.4
Mean number previous live births[c]	0.4	0.7	0.3	0.6
Mean number previous miscarriages[c]	1.3	2.5	0.3	0.8
Mean number previous ovulation induction cycles	0.3	0.3	0.2	0.2
Percent of patients with previous IVF[c]	8%	5%	32%	24%

[a]*Includes two patients with ongoing viable pregnancies at 9 weeks gestation and 29 weeks gestation, who were lost to follow up.*

[b]*Couples were excluded for quitting the program before evaluation or attempting to conceive (52), female baseline FSH level>30mIU/mL, male total sperm count < 1 Million (n=2), or already pregnant before starting treatment (n=3)*

[c] *= There was a statistical difference between groups at $p < 0.05$, by analysis of variance.*

There were a few differences in prior diagnoses (prior to RRM evaluation) between the different outcome groups, as shown in Table 3. Most notably, those who were excluded or withdrew were more likely to have "other" diagnoses, and those who had male factor were more likely to fail to conceive.

The reasons that patients were experiencing infertility were evaluated and analyzed for RRM patients both pre and post assessment and compared to the diagnoses reported for the CDC data set (Table 4). Generally, there was a more detailed diagnosis for RRM patients compared to IVF. For example, categories such as ovulatory dysfunction or uterine factor were further differentiated into 3 and 5 subcategories respectively for RRM patients. The "other" category for the CDC was further defined into 8 subcategories for RRM. There were changes in the diagnosis pre and post RRM assessment, demonstrating that sustained evaluation helped to further define underlying diagnoses. For example, 24% of patients had unexplained infertility pre-assessment and only 1% post assessment. Zero patients had a diagnosis of corpus luteum deficiency, endometritis or hypoandrogenism before RRM assessment but 71%, 17% and 31% respectively had the diagnosis after RRM assessment. There were increases after RRM assessment in the proportion of couples diagnosed with ovulatory dysfunction, endometriosis, insulin resistance, symptoms of endorphin deficiency, endometritis, and hypothyroidism.

Of the 187 patients who underwent treatment, 28% had a previous live birth, 30% had a previous miscarriage and 42% had never conceived. 19% (35/187) had 80 previous IVF cycles, 2.3 $\pm$ 1.6 cycles per couple. RRM treated 187 couples with 52% (98/187) conceiving. Further, 41% (77/187) had a documented live birth and 2 had ongoing viability at weeks 9 and 29 but were lost to follow up and subsequently excluded from these results. There were 75 singletons and 2 sets of twins, producing 79 confirmed babies. Time to conception for live birth patients averaged 12 $\pm$ 8 months. The average birth weight was 3422g (7lb 9oz) and average weeks' gestation at delivery was 39 $\pm$ 1.5 weeks. Both sets of twins and 4% of singleton babies were born preterm (within 33-37 weeks; actual range 34.6-35 weeks) but none were very premature ($\leq$ 32 weeks). 5.3% (4/75) of singleton babies had low birth weight (less than 2,500 grams).

Table 3. Diagnoses prior to RRM evaluation at the Dublin Clinic in 2019, by pregnancy outcome, or exclusion from study.

Diagnosis Pre-RRM Assessment	Live Birth[a]	Mis-carried	Failed to conceive	Excluded or withdrew
Unexplained	25%	32%	22%	23%
Recurrent miscarriage [b]	31%	37%	2%	16%
Ovulatory dysfunction	15%	11%	22%	21%
PCOS	13%	21%	10%	11%
Diminished ovarian reserve	19%	26%	19%	21%
FSH >10 mIU/ml [b]	1%	16%	1%	10%
Male factor [b]	14%	0%	24%	15%
Endometriosis	8%	5%	12%	11%
Hydrosalpinx	1%	0%	0%	3%
Blocked tubes	3%	0%	7%	0%
Uterine polyp	0%	0%	6%	2%
Uterine fibroid	5%	5%	2%	5%
Adenomyosis	0%	0%	0%	2%
Other [b]	0%	5%	2%	11%
PID	0%	0%	1%	6%
Hypothyroid	6%	0%	7%	10%
Hyperprolactinemia	4%	5%	3%	3%
Insulin resistance	1%	0%	1%	3%
Immune	0%	0%	3%	3%

a = Includes two patients lost to follow-up
b = There was a statistical difference between groups at $p < 0.05$, by Fisher's exact test.
Abbreviations PCOS = Polycystic Ovarian Disease; DOR = Diminished Ovarian Reserve; FSH = Follicle Stimulating Hormone; PID = Pelvic Inflammatory Disease

Table 4. Diagnostic reasons for infertility for CDC IVF registry data in 2019, and both pre and post restorative reproductive medicine (RRM) assessment conducted at the Dublin Clinic, 2019.

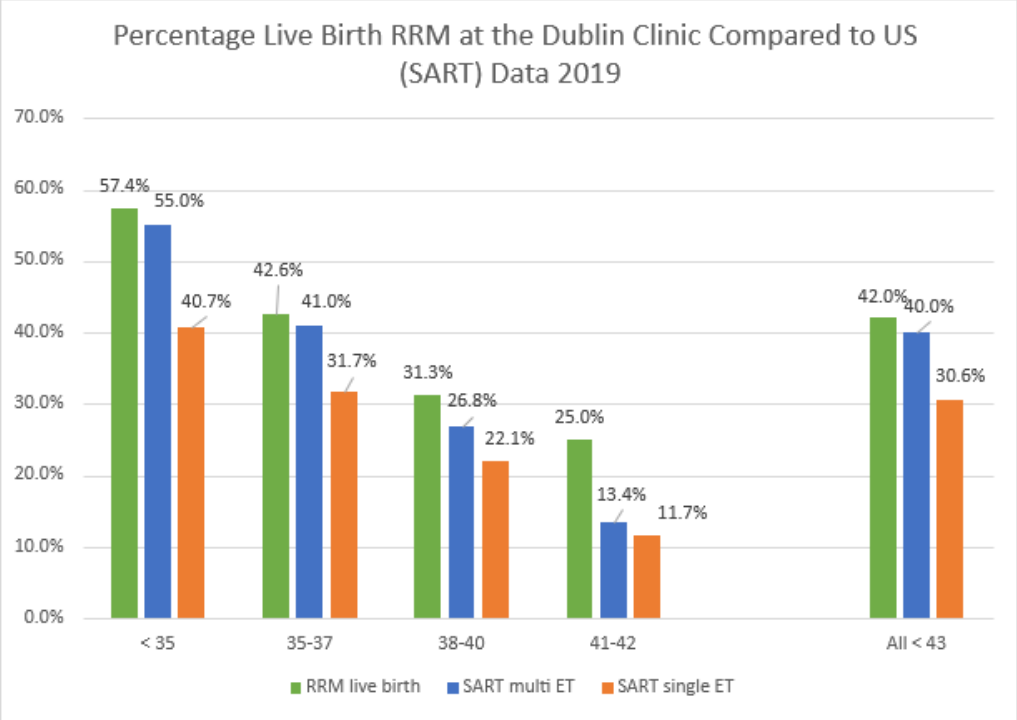
Diagnosis	CDC	Pre RRM assessment	Post RRM assessment
Unexplained	11%	24%	1%
Recurrent miscarriage	6%	17%	11%
Ovulatory dysfunction	14%	19%	76%
Polycystic ovarian syndrome	Not reported	12%	12%
Corpus luteum deficiency	Not reported	0%	71%
Diminished ovarian reserve	29%	20%	20%
Follicle stimulating hormone >10 mIU/ml	Not reported	4%	4%
Male factor	27%	16%	20%
Elevated sperm DNA fragmentation	Not reported	0%	10%
Endometriosis	7%	10%	25%
Tubal factor	10%		
Hydrosalpinx	Not reported	1%	0%
Blocked tubes	Not reported	3%	2%
Uterine factor	6%		
Asherman's syndrome	Not reported	0%	1%
Uterine polyps	Not reported	2%	2%
Uterine fibroids	Not reported	4%	3%
Uterine septum	Not reported	0%	3%
Adenomyosis	Not reported	1%	1%
Other	27%	4%	12%
Pelvic inflammatory disease	Not reported	2%	3%
Hypothyroidism	Not reported	7%	24%
Hyperprolactinemia	Not reported	4%	1%
Insulin resistance	Not reported	2%	16%
Hypoandrogenism	Not reported	0%	31%
Endometritis (including brown post menstrual spotting)	Not reported	0%	17%
Symptoms of clinical endorphin deficiency	Not reported	1%	67%
Immune (natural killer cell, LAD)	Not reported	2%	9%

Abbreviations: RRM = Restorative Reproductive Medicine; CDC = Centers for Disease Control and Prevention; DNA = Deoxyribonucleic Acid; LAD = Leukocyte Adhesion Deficiency

When we compared RRM births to the IVF databases across all age groups, we excluded the older age groups where the number of older patients for RRM was low. In these comparisons, the crude RRM percentages were comparable

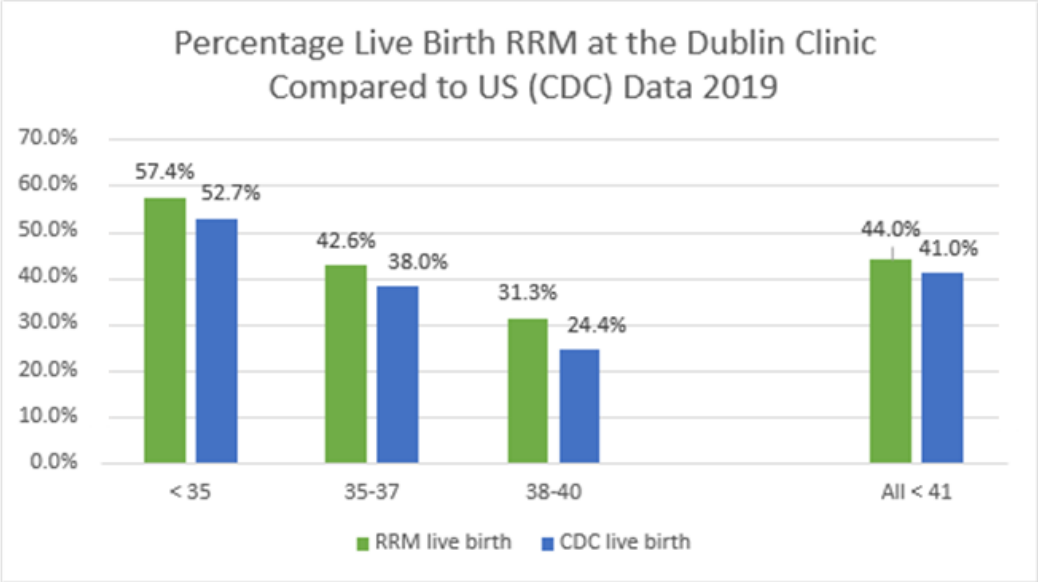
to SART (42.0% RRM vs 40% SART, patients < 43 yrs, Figure 1) and CDC (44.0% RRM vs 41% CDC, patients <41 years, Figure 2) for one IVF retrieval utilizing multiple embryo transfer attempts. HFEA and SART data, which only utilized one embryo transfer, had a lower percentage live birth at 24.4% (Figure 3) and 30.6% (Figure 1) respectively, Without the raw data from these databases, we could not test the comparisons statistically. By excluding data from older patients, the comparisons were more closely matched for female age since the IVF databases had larger numbers of much older patients compared to RRM patients in 2019. As apparent in the figures, each registry reports the age groups slightly differently.

Figure 1. RRM live birth at the Dublin Clinic compared to IVF, US (SART) Data, 2019[a]



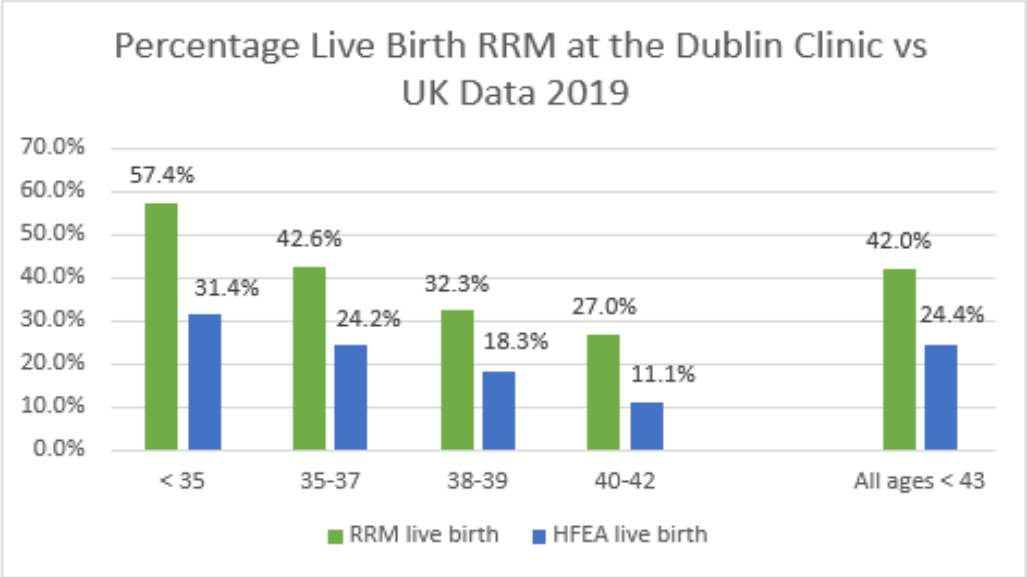
[a]176 RRM patients followed up to 32 months compared to one IVF intended retrieval attempt with a single fresh (117,306 patient treatment cycles) or fresh plus freeze-thaw embryo transfers (117,530 patient treatment cycles). IVF data from United States Society for Assisted Reproductive Technology (SART). Patients older than 42 were excluded from the figure.

Figure 2. RRM live birth at the Dublin Clinic compared to IVF, US (CDC) Data, 2019



156 RRM patients followed up to 32 months compared to one IVF intended retrieval attempt with one or more embryo transfers (111,536 patient treatment cycles). IVF data from United States Centers for Disease Control (CDC). Patients older than 40 were excluded from the figure.

Figure 3. RRM live birth at the Dublin Clinic compared to IVF, UK (HFEA) Data, 2019



176 RRM patients followed up to 32 months compared to one IVF intended retrieval attempt with one embryo transfer (33,861 patient treatment cycles). IVF data from United Kingdom Human Fertilization and Embryology Authority (HFEA). Patients older than 42 were excluded from the figure.

Multiple pregnancies (twins) for RRM patients occurred in 2/79 or 2.5% of confirmed live births and for IVF patients the percentage was 6.1% (CDC), 6.8% (SART), and 7% (HFEA). SART also reported the percentage of pregnancies that result in triplets or higher order at 0.12%. The 75 confirmed singleton pregnancies from RRM resulted in 4% preterm deliveries and all pregnancies resulted in 6.5% preterm deliveries compared to preterm deliveries for SART (14.8% all pregnancies) and CDC (11.8%, singleton pregnancies only). Of the singleton RRM pregnancies, 5.3%

(4/75) were born with a low birth weight and 3 out of 4 of the twin babies had a low birth weight. The CDC reported that 11.8% of singleton births from singleton pregnancies had low birth weight but the category of very low birth weight was not reported. In addition, singleton pregnancies from established multiple pregnancies, meaning pregnancies that were reduced intentionally or spontaneously to a single fetus, had a 24.5% low birth weight and 23.7% were born pre-term.

The RRM evaluation and treatments applied pre-conception and during pregnancy can be found in Tables 5 and 6, respectively. The treatments most often used prior to conception were follicle stimulation and tracking, HCG trigger shots, HCG during the luteal phase, and low dose naltrexone, all in over 70% of patients (Table 5). Luteal phase progesterone was used in 40% of patients. Hysteroscopic surgery was used in 43% and laparoscopy 40% of patients. Of the patients who had these surgeries, 60% were subsequently diagnosed with endometriosis.

Table 5. Pre-conception restorative reproductive medicine (RRM) medical and surgical evaluation and treatments in Dublin Clinic patients, 2019

Treatment	**Percent**
Follicle tracking	76%
Hysterosalpingography	6%
Saline infusion sonography	1%
Laparoscopy	40%
Hysteroscopy	43%
Uterine surgery	3%
Tubal surgery	0%
Follicle stimulation	77%
Prednisolone/dexamethasone	9%
HCG ovulation trigger shot	73%
Luteal phase HCG	72%
Luteal phase progesterone	40%
Luteal phase estradiol	4%
Low dose naltrexone	71%
Thyroid treatment	25%
Metformin	16%
Myoinositol	21%
DHEA	29%
Antibiotics	23%
Sympathomimetic medication	14%
Estradiol to sensitize follicle stimulating hormone (FSH) rece	3%
Misoprostol to facilitate follicle rupture	14%

Table 6. Treatments during pregnancy and the trimester when treatment was discontinued, 2019 Dublin Clinic RRM patients.

Treatment	First trimester	Second trimester	Third trimester	All
Progesterone	43%	21%	31%	95%
Thyroid therapy	2%	1%	17%	20%
Low dose naltrexone	14%	7%	37%	58%
Metformin	4%	1%	12%	17%
Myoinositol	3%	1%	5%	9%
Prednisolone	21%	2%	2%	25%
DHEA	16%	12%	9%	37%
Anticoagulants	4%	0%	12%	16%
Estrogen	0%	0%	0%	0%
Sympathomimetic medication	3%	0%	2%	5%
Antibiotics	0%	0%	0%	0%
HCG	0%	0%	0%	0%
Other	2%	0%	0%	2%

The most frequently applied treatment post-conception was progesterone supplementation in 95% of patients, followed by low dose naltrexone which was utilized in 58% and DHEA in 37% of patients, respectively (Table 6). There were no statistically significant differences in treatment between patients conceiving and having a live birth compared to those who conceived and miscarried (Data not shown).

DISCUSSION

The NeoFertility practice in Dublin, Ireland is known as a specialized clinic for infertility and recurrent miscarriage. The clinic sees patients with more advanced or complex reproductive health issues but does not use in-vitro fertilization, nor intrauterine insemination. Patients qualify for RRM treatment at the clinic if the man has a sperm count of at least 1 million per ml, the woman has an FSH level less than 30 mIU/ml, and she has at least one fallopian tube that is patent after surgery. There were 249 patients that attended an introductory appointment in 2019 and 62 of the patients (25%) did not advance with treatment protocols. The initial RRM consultation is 45 minutes long, during which the process of treatment is explained in detail, together with an estimation of the chances of success. Couples are asked to pay for a treatment plan equivalent to half the cost of an IVF treatment cycle and commit to up to 12 optimal treatment cycles.

Most of those who did not proceed with evaluation and treatment would have been eligible to proceed in the clinic. They were not found to be significantly different than the other groups in most demographic characteristics or prior diagnoses (Tables 2 and 3). It is common for patients experiencing infertility to discontinue treatment. In one large study, the incidence of discontinuing treatment with IVF was found to be over 65% for patients, who cited psychological or financial burden and/or stress as the main reasons for this[10]. However, in our cohort, 2% (5/249) of couples discontinued once they had started RRM treatment, indicating that most discontinuation is mostly “up front” after the first consultation.

Not surprisingly, female patients who subsequently had a live birth were on average younger and had been trying to conceive for fewer months. RRM couples who miscarried had more prior pregnancies and miscarriages. Couples who failed to conceive had the lowest number of previous pregnancies and a higher percentage of patients who previously pursued IVF (Table 2).

The mean female age for the RRM clinic was similar to that of the IVF registries (Table 1). Unfortunately, data on several key prognostic factors, such as parity, prior IVF treatment, prior time trying to conceive were not available for the IVF registries, which limits our ability to compare between the RRM patients and the IVF registry patients.

The analysis of the reasons or diagnoses for infertility both pre and post RRM assessment along with a comparison to those reported by the CDC registry[6] (Table 4) provided insight into the rationale for multi-factorial treatment for infertility and suggest one reason why RRM may be different from conventional IVF, at least as reported in the registries. Our RRM cohort had a detailed list of potential underlying diagnoses, compared to the CDC database, consistent with other published RRM results.[11, 12] After RRM evaluation, it is unusual for patients to have a diagnosis of “unexplained” infertility. Although IVF is a relatively homogeneous set of procedures across diagnoses, there are still differences in the effectiveness of IVF (crude live birth rates) based on the diagnosis. These are reported in the SART database for 2019 in Table 7. For most age groups, live birth outcomes for patients with diminished ovarian reserve are the lowest and couples with male factor have the highest percentage of live

births. In our opinion, these differences point to the value of accurate (and more detailed) diagnosis and the need for targeted treatment protocols.

We chose to only utilize crude percentage live birth in this report for comparisons because this is the measure reported in the IVF registries. Across all female age groups, the RRM percentage live birth rate was 41%. For each female age group, the crude percentage of live births in RRM patients were similar to the SART (Figure 1) and CDC (Figure 2) registries, which included multiple embryo transfer attempts after one IVF retrieval. Compared to the SART (Figure 1) and HFEA (Figure 3) registry data, which only include one embryo transfer after the retrieval, the RRM percentage live births appear to be higher. Notably, in this study, of patients who had one live birth and engaged with the clinic to seek another pregnancy, 74% (26/35) achieved a second RRM live birth.

Table 7. IVF Live birth rates per single embryo transfer, by diagnosis and female age, Society for Assisted Reproductive Technology (SART) registry, filtered for 2019.

Diagnosis	<35	35-37	38-40	41-42	>42
All	40.7%	31.7%	22.1%	11.7%	3.9%
Endometriosis	41.5%	28.5%	24.1%	10.8%	0.0%
Diminished ovarian reserve	26.0%	22.4%	15.7%	9.7%	2.6%
Multiple female	33.4%	27.5%	19.7%	9.8%	3.8%
Ovulatory dysfunction	41.3%	35%	22.2%	16%	NA
Tubal factor	41.6%	34.1%	26.0%	11.9%	4.6%
Uterine factor	35.1%	28.1%	20.0%	13.8%	6.6%
Female and male factor	41.7%	31.2%	21.1%	12.2%	5.0%
Male factor	45.1%	37.5%	27.9%	17.1%	6.3%
Other factor	39.4%	32.2%	26.1%	12.7%	5.3%
Unknown	43%	36.6%	26.9%	17.1%	5.2%

In the RRM patients, conception took an average of 12 months. The longest patient took 32 months (2 years, 8 months) to conceive. This live birth rate and time to conception is consistent with previous RRM reports, as summarized in Table 8. The time to conception was not reported for patients in the IVF databases but it is likely shorter. RRM is based on the concept that infertility is a sign of chronic disease caused by multiple underlying chronic health conditions or diagnoses. It follows that it takes some time to reverse the impact of chronic disease sufficiently to conceive and have a healthy birth. Also, because the number of eggs collected from one IVF retrieval is most often 6-15,[16] or an average of 9,[17] we feel it's reasonable to compare one IVF retrieval, with associated embryo transfers, to a longer period of cumulative approximately monthly ovulations of usually one egg at a time.

The incidence of twins was 2.5% (2/79) for RRM and there were no higher order pregnancies, whereas the incidence of twins was 6-7% for all three IVF databases and there were also some higher order pregnancies. IVF pregnancies had more than twice as many pre-term deliveries compared to our RRM cohort, (11.1% vs 4% for singleton pregnancies and 14.4% vs 6.5% for all pregnancies). We believe that the additional financial and health burden associated with multiple gestation and premature delivery needs to be weighed heavily in the analysis of costs and benefits associated with fertility treatment, particularly for IVF. We are not able to compare financial costs systematically between RRM and IVF; however, based on fees listed on websites for the Dublin clinic and a conventional IVF program in Ireland, the RRM treatment plan is currently estimated to be less than half of the cost of one IVF treatment cycle. Future research should undertake formal cost effectiveness analyses.

Table 8. Previously published and current study RRM outcomes for infertility: live birth (unadjusted percentage) and cumulative period of follow-up.

Study	Number of couples	Live birth, crude percentage	Cumulative months
Stanford et al., 2008[14]	1072	25.5%	24
Tham et al., 2012[13]	108	38.0%	24
Boyle et al., 2018[12]	403 [a]	18.4%	24
Stanford et al., 2021[10]	370	17.8%	24
Stanford et al., 2022[11]	834	44.2%	36
Current Study	187	41.2%	32

[a]all patients in this study had previously received and failed in vitro fertilization (IVF)

The goal with RRM is to find and treat, often several factors that are contributing to infertility which presents more like a chronic illness and therefore needs multiple, sustained interventions over time to restore optimal health and normal function.[11,12] Although there are similarities between RRM, pre-IVF and IVF treatments, there are important differences. From our perspective, important differences in how the treatments are performed and monitored are outlined in Table 9, which we present to be illustrative and not necessarily fully representative or comprehensive. With RRM we can assess and monitor a woman's reproductive health by teaching her how to precisely record her biological markers of fertility with cycle tracking, and through targeted treatments, restore healthy ovulation.[19] Similarly, we investigate multiple avenues to restore healthy spermatogenesis.

Details of multiple treatments that are targeted for different underlying conditions prior to conception were given in Table 5. In addition, we have found that it is critical to continue appropriate monitoring and targeted treatment once pregnancy is established, as shown in Table 6. Almost every patient received progesterone supplementation, but also many received additional treatments during pregnancy.[20]

In our anecdotal experience, patients frequently report that IVF was previously recommended to them without identifying or treating multiple underlying health issues. Without fully addressing underlying health issues, resulting pregnancies may be less healthy.[15,21] Anecdotally, we find that an additional benefit of RRM is that it can address underlying health concerns and improve fatigue, premenstrual mood symptoms, anxiety, dysmenorrhea, and dyspareunia, even for patients who do not conceive.

A key component of successful RRM treatment is access to skilled laparoscopic surgeons, most especially to identify and treat endometriosis which is common in women with infertility.[22] Sometimes the only symptom of endometriosis is infertility or recurrent miscarriage.[23] The important role of surgery was highlighted in our study by the observation that 60% of the patients who had laparoscopy or hysteroscopy were subsequently diagnosed with endometriosis.

Table 9. Common treatments used in Dublin Clinic for restorative reproductive medicine (RRM) in comparison to common conventional treatments preceding or during in vitro fertilization (IVF). (Comparisons are illustrative, not fully comprehensive or necessarily representative.)

Treatment	RRM	Conventional preceding IVF	IVF
Ovulation tracking	Multiple biomarker tracking with cycle tracking app, also serial ultrasounds when indicated for monitoring ovulation stimulation.	Variable ovulation monitoring, which may include some biomarkers or serial ultrasound.	Serial ultrasounds for monitoring ovulation stimulation.
Follicle stimulation goals, (Letrozole, Clomiphene, FSH)	One dominant follicle, tracked by ultrasound, hormones and formal biomarker monitoring for 12-18 cycles.	1-2 dominant follicles, tracked by ultrasound, hormones, and urine luteinizing hormone for up to 3-6 cycles.	Includes GnRH analogs tracked by hormones and ultrasound. Supra-physiologic process often producing 6-15 dominant follicles.
HCG trigger shot	Used to assist follicular release (usually single follicle).	Used to assist follicular release (single or multiple follicles).	Used to promote follicular maturity of many follicles, prior to egg retrieval.
Fertilization	In-vivo natural	In-vivo natural	In-vitro or sperm injected
Luteal phase and early pregnancy hormonal support (P4, HCG, DHEA)	Closely monitored and treated	Variable support, often including P4	Variable support, usually including P4
Thyroid	Monitored and treated	Monitored and treated	Treated if previously detected
Hypo or Hyper androgenism	Closely monitored and treated	Monitored and treated	Treated if previously detected
Insulin resistance	Closely monitored and treated	Monitored and treated	Treated if previously detected
Low dose naltrexone	Used for symptoms suggesting endorphin deficiency	Not used	Not used
Antibiotics for female reproductive tract infection	Aggressively monitored and treated	Treated if previously detected	Treated if previously detected
Use of gametes	In-vivo natural	Sperm are handled outside the body for intrauterine insemination.	Sperm and eggs are handled outside the body for fertilization.
Use of embryos	In-vivo natural	In-vivo natural	Embryos may be graded, selected, frozen, stored, or discarded.

Abbreviations: RRM = restorative reproductive medicine; IVF = in vitro fertilization; FSH = follicle stimulating hormone: GnRH = gonadotropin releasing hormone; HCG = human chorionic gonadotropin; DHEA = dehydroepiandrosterone; P4 = progesterone

CONCLUSIONS

Many couples with infertility can be treated for underlying health issues and conceive naturally through RRM. The crude percentage of live birth, stratified for woman's age, is very similar to the reported success of a single cycle of IVF with autologous gametes (i.e., no donor eggs) across 3 different IVF databases in the US and UK. On average, most couples conceive within 12 months. Couples conceiving with RRM had fewer multiple pregnancies, pre-term births and low birth weight babies.

The comparisons of these RRM patients to the CDC, SART and HFEA registries are preliminary benchmarks. They are limited by a relatively small sample size for the RRM patients, and the lack of important prognostic data (other than female age) for the IVF registry patients. There is an urgent need for prospective studies with full prognostic data to make a proper comparison of RRM and IVF outcomes. Ultimately, we propose that with proper training of dedicated RRM physicians and additional research, RRM may improve a couple's chance of having a healthy pregnancy and reduce the number seeking IVF to address infertility.[1,24]

CONFLICT OF INTEREST DISCLOSURES

The authors declare they have no conflicts of interest.

ETHICAL APPROVAL

Ethical approval for this study was received from the Beacon Hospital Research Institute ethics committee in January 2025 allowing de-identified retrospective analysis of the results without requiring informed consent.

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DATA AVAILABILITY

Data for each of the IVF databases are available to the public and referenced. Data from the NeoFertility clinic is de-identified but can be accessed by contacting the principal investigator.

AUTHORS' CONTRIBUTIONS

All authors agree to be accountable for all aspects of the work including accuracy or integrity.

Boyle: *Principal investigator and data acquisition*

Boyle and Turczynski: *Design, analysis, interpretation, and final draft approval*

Boyle, Turczynski, Toth, Minjeur: *Drafting the work, reviewing it critically for important intellectual content*

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