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# A UK National Survey for patients and stakeholders: Outcomes of 319,105 IVF/ICSI and 30,669 IUI treatment cycles

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<td>28-Sep-2019</td>
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Abstract

Objective To compare success rates, associated risks and cost-effectiveness between IUI and IVF.

Design Retrospective observational study of the world’s largest regulated dataset overriding the limitations of RCTs.

Data sources Human Fertilisation and Embryology Authority Freedom of Information (FOI) Request for 2012-2016 for in vitro fertilisation (IVF) and intrauterine insemination (IUI) as practiced.

Study selection This is a retrospective observational study of 319,105 IVF/ICSI and 30,669 IUI cycles performed between 2012 and 2016 in the UK. Direct cost for maternal and neonatal expenditure per LB was constructed using the Cost of Multiple Birth (COMBS) model, with inflation-adjusted pricing using Bank of England index-linked data. A second direct cost analysis evaluating the incremental cost effective ration (ICER) was modelled on the 2016 national mean (baseline) IVF and IUI success rates.

Results This largest comprehensive analysis integrating success, risks and costs at a national level shows IUI is safer and more cost effective than IVF treatment. IUI success is much closer to IVF than previously considered, while IVF remains a significant source of MGP. Uniquely, reliable levels of MGP, OHSS, fetal reductions and terminations associated with IVF are revealed. IUI is more cost effective in delivering 1 LB and this effectiveness is maintained against top-end IVF clinics, which lose residual benefits through increased MGP and tariffs. The huge IVF maternal and neonatal cost burden has remained invisible so far and is passed onto the UK NHS.

Conclusion IUI should be practiced before IVF. IUI success is much closer to IVF than previously considered, more cost effective in delivering 1 LB, cost efficient towards maternal and neonatal care, less risky for mothers and babies in terms of MGP, OHSS, fetal reduction and termination.
Strengths and limitations of this study

- Retrospective cohort study of one of the largest aggregate UK statutory national data on 319,105 IVF/ICSI and 30669 IUI cycles from 2012-2016.

- Data obtained under FOI overcome selection biases and allows for the first integrated analyses of success, risks and costs to achieve 1 LB from IUI and IVF procedures.

- Cost analyses were performed by specialist financial analysts on two fronts; cost efficiency to produce 1 LB and secondly the real cost burden to the nation due multiple births. Contrary to fertility industry belief, it was cheaper to gain to 1 LB from IUI compared to IVF procedure. Multiple births from IVF and not IUI present an acute latent cost burden for the national health system (NHS).

- For the first time the level of terminations in IVF for social/psychological reasons is disclosed due to a large scale FOI request.

- Limitations stem from a lack of data available from the statutory body such as stimulation regime, numbers of cycles undertaken by each patient or IVF add-on procedures undertaken which could have added value for academic and clinical purpose. However, these limitations would not alter the conclusions reached to be of significant value for the stakeholders, patients and healthcare providers commissioning fertility services.

Introduction

There is limited comprehensive and direct comparison between intrauterine insemination (IUI) and in-vitro fertilisation (IVF) treatments at national level encompassing success, risk and cost.

Information on different assisted reproductive techniques (ART) success, risks, failures and costs can be challenging for patients, politicians and healthcare stakeholders paying for services. IVF success claims have an overbearing presence on social media and in patient forums to such an extent that other ART such as IUI are relegated or dismissed outright. The HFEA website appears wholly negative towards IUI suggesting poor success, uncontrolled multiple births and a high cost of failure over several cycles.

The UK National Institute of Health and Care Excellence examined the effectiveness of 25mg clomiphene citrate with IUI against expectant management and found no differences, but then without comparative IUI and IVF evidence, recommended removing IUI altogether and replacing it with three cycles of IVF.

A recent systematic review and meta-analysis including 10 randomised controlled trials (RCTs) comparing IUI and IVF found no difference in safety and effectiveness between treatments. The overall quality of the evidence provided by RCTs has been low or very low for all comparisons. Subsequent well designed RCTs support IUI over IVF.
There are no large national data analyses. A European meta-analysis relying on voluntary data submission identified 1 million underreported cycles from 6 million cycles which would compromise interpretations of the data. Statutory National data analysis removes the selection bias of individual studies and the incompleteness of voluntary data submissions.

We aimed to compare the effectiveness of IUI with IVF as practiced in the UK over a 5 year period where full data was available. The hypothesis tested was that IUI would be associated with better outcomes than IVF in terms of pregnancy success rates, risk of complications and costs.

**Methods**

**Study design and participants**

This is a retrospective observational study of 319,105 IVF/ICSI and 30669 IUI cycles performed between 2012 and 2016 in the UK. Data were obtained from the UK-regulated HFEA database. The data was collected entirely by HFEA staff under FOI including LB per cycle, multiple births, OHSS, fetal reduction, terminations and level of government funded IVF cycles for IVF and IUI. Other clinic data was available on the HFEA website.

Direct cost for maternal and neonatal expenditure per LB was constructed using the COMBS model as previously described, with inflation-adjusted pricing using Bank of England index-linked data. The final figures were derived from the number of IUI and IVF cycles performed in 2016, against the level of MGP produced. Twin and triplet analyses allows for an individualised cost calculation for every birth component to be applied evenly and accurately for maternal and neonatal care based on the COMBS model.

A second direct cost analysis evaluating the ICER was modelled on the 2016 national mean (baseline) IVF and IUI success rates. An algorithm was developed to establish the relationships between IUI and IVF at prevailing baseline LBR and costs to determine cost effectiveness from clinics with variable success rates.

The relationship between IUI and IVF clinics with high LBR was considered alongside the standard performing clinics using the HFEA database and for IUI additional in-house (North Middlesex University Hospital, NMUH) data was available. The calculations were also performed using the mean 2016 IVF tariff. The common tariffs per treatment cycle for IUI at £800-£1300 and £3,500-5000 (HFEA mean £4699/cycle) were entered into our algorithm model, while IVF outliers for success and tariffs were considered separately.

**Randomisation and masking**

The very large data relates to actual and overall national practice and overrides RCT requirements for stratification or masking where small numbers are considered. RCTs are also associated with selected population and involve experimental design to control external factors.
Limitation of the FOI dataset is the absence of information on ovarian stimulation regimes, number of patients treated, mean number of treatment cycles per patient, cause of subfertility, extent of eSET, previous ART, oocyte retrieval complications, birth weight, sex ratios, gestational age and ectopic and molar pregnancies. Repeated FOI request could generate small differences in data given the enormity of the data gathering exercise. Unfactored also are the costs due to OHSS, fetal reduction, termination, sperm/embryo freezing, embryo culture, add on techniques and work absenteeism.

Procedures
The procedures are fully described under methods section. The procedure of data collection was through FOI requests from the UK HFEA collecting information as part of its regulatory remit and for the purpose of issuing a licence to clinics to operate. There is therefore no scope for clinics to selectively submit or withhold their activities or outcome data. The HFEA provided a summary of the data in tabulated form which also restricts further interrogation of data or the manner in which statistics can be performed. The HFEA also provided details to reveal the nature of pregnancy terminations.

None of the authors could influence the data set or the manner in which data could further inclusion/exclusion choices, as this was handed over under FOI by the HFEA. No UK clinic could selectively submit data to the HFEA. Submission is a statutory obligation, resulting in revocation of the clinic licence for serious breaches.

Outcomes
The primary outcome was LB per cycle, MGP levels, OHSS, fetal reduction and terminations. The reasons for terminations were disclosed. The total cost of maternal and neonatal care through IUI and IVF for 2016 was calculated using actual 2016 figures derived from the COMBS model and inflation adjusted figures from the Bank of England data. ICER, to deliver 1 LB was obtained for real IUI and IVF activities and actual tariffs paid by patients. The percentage of IVF cycles was disclosed by the HFEA, and the level of funded treatments performed by NHS-funded private IVF clinics (which are not accountable under FOI laws).

Statistical analysis
The proportions with the standard error (SE) were calculated for the given outcome. The 95% CI was calculated as +/- 1.96 SE. Absolute and relative differences in risk were calculated, together with their SE. p values were calculated from the ratio of the measured absolute difference to the standard error, assuming variation to be normally distributed. Analysis was performed for main outcome measures such as LB rates, MGP rates, market worth of interventions against maternal and neonatal costs, and cost to achieve 1 LB and permutation thereof. Within IVF and IUI activity trends were calculated using Graphpad Prism software (version 8). For each exposure and outcome studied, relative risks were calculated using Medcalc software (https://www.medcalc.org/calc/relative_risk.php). For each comparison, the standard error was calculated for the difference in absolute risk, and a two-tailed z-score calculated. 5% (p=0.05) was taken as the limit of significance.
Results

Data from the UK HFEA database between 2012-2016, showed an overall 10.4-fold increased use of IVF compared to IUI. The downward trend in IUI cycles was statistically significant $R^2$ of 0.89 ($p<0.05$) (Table 1), whereas there was a statistically significant increase in IVF cycle showing a significant slope $R^2$ of 0.99 ($p<0.001$) (Table 1).

There was a statistically significant improvement in LBR (live birth rate) for IVF between 2012 and 2016 [2012: 25.47% (25.12-25.82); 2016: 27.32% (26.98-27.65). Absolute difference: 1.84% (1.36 -2.33). RR: 1.07 (1.05-1.09) $p<0.001$]. The improvement from 25% to 27% LB/cycle for IVF remains small.

There was no change in IUI success over the same period [2012: 11.66% (10.93-12.39; 2016: 12.10% (11.09-12.10). The absolute difference was 0.43% (-0.81-1.67). RR: 1.04 (0.93-1.15) $p=0.25$ (Table 1). IVF had a significantly higher LB/cycle compared to IUI [IVF: 26.96% (26.81-27.12); IUI: 11.49% (11.13-11.85). Absolute difference: 15.47% (15.09-15.86). RR: 2.35 (2.27-2.42) $p<0.001$]. An additional birth will be achieved for every 6.5 IVF cycles compared to IUI (NNT=6.46) (Table 1).

The rate of MGP as a proportion of all births was significantly higher after IVF than IUI [IVF: 13.88% (13.65-14.11); IUI: 9.59% (8.62-10.56) with absolute difference: 4.29% (3.29-5.29). RR: 1.45 (1.31-1.60) $p<0.001$]. An additional multiple pregnancy will occur for every 23 IVF pregnancies compared to IUI (NNT = 23.31) (Table 1). Data from 2012-2016 (Table 1) reveal other risks such as OHSS, fetal reduction and terminations and the level of government funded IVF cycles and additionally the level commissioned through private IVF clinics. As part of the risk factor association, reasons for terminations were additionally disclosed by the HFEA. Results from Table 1 is discussed in detail.

Financial calculation

Two types of financial analyses are included (a) the national maternal and neonatal care cost burden and (b) ICER, to deliver 1 LB per cycle (Fig 1 and 2).

Size of maternal and neonatal cost: Based on HFEA 2012-2016 figures 1 LB from IUI is made up of singleton: twin: triplet in the components 91.25: 7.90: 0.85 respectively, whereas for IVF the singleton component is reduced in the proportion 86.21: 13.65: 0.14. Twin and triplet figures were number of sets, rather than individual babies. For 2016, maternal and neonatal, adapted from COMBS model and index link adjusted for 2016, the cost (£) per birth events factoring the singleton, twin and triplet cost was £4945, £13618, £48300 respectively. Associated with maternal and neonatal cost for one IUI and IVF baby was £6000.406525 and £6186.538342 respectively.

Financial size of the 2016 UK IVF and IUI industry against the MGP risk cost burden for the NHS

The IVF maternal and neonatal cost for 2016 was £115,082,017 against the IVF market value of £238,346,500 to £340,495,000 for 2016. In contrast, for IUI the maternal and neonatal risk burden from IUI was £2,940,196 against the IUI market value of £3,240,800 - 5,266,300. The maternal and neonatal risk burden due to IVF is 39-fold higher than IUI, against a 10.4-fold greater IVF activity over IUI. The size of maternal and neonatal care for the UK from IVF or IUI could not be confirmed by The Department of Health and Social Care’s (FOI Response FOI-1160477).

To understand the relationships between high LBR IUI and IVF clinics, data from North Middlesex University Hospital (NMUH) IUI at £800 tariff was utilised. Between 2014-18:
672 cycles, 364 women, 119 pregnancies, 2 twins; PR/cycle 17.7%/cycle; PR/woman 32.7%/woman; LB/Woman 28.7%/woman; LB/cycle 15.60%; 2 twins, no severe to moderate OHSS reportable to the HFEA, but 7 cases of mild-moderate OHSS not requiring hospitalisation; 63% of all cycles performed using consecutive ejaculation, hMG stimulated with strict cancellation policy for >=3 follicles or OHSS. Against this, typical higher undisclosed IVF clinic results showed 55% LB/cycle and 30% MGP rates from the HFEA database, and which also had typical IVF tariff of £7,000-15,000/cycle. Both sets of data were placed in perspective against standard IVF clinics where the mean success rate for 2016 was 27% LB/cycle and with a mean tariff of £4699.

Table 1: UK IVF and IUI 2012-2016 outcomes

Fig 1 & 2: Economic and financial analyses of IUI versus IVF- direct cost effective analyses to deliver 1 LB based on actual success rates and tariffs for IUI and IVF (see Discussion)

Discussion

Unprecedented levels of actual IVF and IUI practice information emerging from this study have profound implications for the whole field treating subfertile patients. Data summary provided by the HFEA has allowed descriptive comparisons and trends where possible, but limits the use of complex statistics. This is advantageous as alternative interpretations of the data become impossible, thereby removing interest biases. No sample size calculation was required to determine the power at a significance level of 0.05.

This first integrated national scale study confirms previously published data showing better LBR in IVF than in IUI but this difference is much closer than previously considered. IVF has a significantly greater risk for MGP than IUI (p<0.001). IVF is also associated with additional serious risks of OHSS, fetal reduction and terminations which are not evident for IUI. Actual cost to achieve 1 LB from IUI and IVF favors IUI whereas the IVF maternal and neonatal MGP babies cost burden is 39-fold over IUI. These cost burdens have remained hidden from the national health budget, while also confirming IUI should be performed before IVF. Success cannot be looked at separately of risks and costs.

There was 10.4-fold increased use of IVF over IUI with a significant increase in IVF cycles, with declining IUI cycle numbers from 2012 to 2016. This increased IVF activity cannot be justified according to evidence based medicine, given there was no comparative IVF versus IUI data exists and highlighted by NICE. The significantly (P<.05) increase in IVF and concurrent significant decline of IUI cycles (Table 1) coincide with the 2013 NICE guidelines recommending against IUI. This period saw a statistically (p<0.001) improved LBR for IVF, although the difference remained small from 25% to 27% LBR.
Important relationship between IUI and IVF to achieve 1 LB based on actual success rates and tariffs becomes apparent from Table 1, Fig 1 and 2. Baseline IUI: IVF success rates to deliver 1 LB was 2.35:1, much narrower than the RCT reported of 3:1 for IUI: IVF. A small improvement in IUI LBR from 12.1% to 15.6% LBR narrows this equivalence further to 1.73:1, IUI: IVF cycles, with a highly favourable positive cost benefit for IUI over IVF. When considering IVF as a denominator it is easy to forget 3.7 IVF cycles are actually required to achieve a 100% theoretical LB. From these figures it follows 8.69 IUI cycles at 12.1% LBR or 6.4 cycle for a 15.6% LBR IUI NMUH clinic are needed to theoretically achieve 100% LB. Patients or stakeholders therefore require to budget for these numbers of cycles when commissioning fertility treatments. Against prevailing tariffs IUI always has lower overall costs than IVF in commissioning treatment to achieve 1 LB. Patients should be informed that IUI success is closer to IVF but without the added risks to mothers and babies, the cost burden to the health care system of which are excessive for IVF. Despite the focus on IUI against IVF, the relationship between ordinary and high success IVF clinics seems curiously avoided.

Mean-IVF clinics (27% LBR, MGP 15%) against as high performing IVF clinic (55% LBR, MGP 30%) have a 2.04:1 relationship but higher IVF clinics have riskier (2.2:1) outcomes for mother and baby. Factoring tariffs alone, IUI is cheaper than IVF while also delivering lesser risks and perinatal complications for both mothers and babies. Higher IVF outcomes lose any benefits through higher tariffs and doubled MGP levels against IUI and against standard performing IVF clinics. The actual cost benefits are displayed in Fig 1 and Fig 2 which study the ICER to deliver 1 LB at various success rates and tariffs.

A recent RCT shows that after 3-4 years unexplained infertility randomised for three cycles of IUI (CC) or expectant management a three-fold improvement in outcome in LBR from 31% and 9% is seen. IUI LB/cycle probabilities ranged from 21.4% to 5.1% dependent on age, cycle number and previous parity, with a MGP of 5.4%. IUI was also effective on LBR (OR 1.95 (1.10 to 3.44) (95% CI)) when compared with intercourse or expectant management in a stimulated cycle. Currently in most clinics, IUI suited cases are now receiving IVF treatments or are further aided with non-evidenced based add-on techniques. IUI success rates appear to face downward pressures from IVF clinics by managing difficult cases through IUI. So far no reliable national figures exist for the levels of different risks for patients undergoing IVF and IUI to help them towards a journey of making informed decisions or to help clinicians counsel their patients. With this large database, the MGP rate as a proportion of all births was significantly higher following IVF than following IUI (RR: 1.45 (1.31-1.60) p<0.001]). This fact contradicts popular belief that IUI being the source of uncontrolled MGP. The rate of twins was also significantly higher following IVF [RR: 1.58, p<0.001]). There was 0.2% fetal reductions performed for IVF and none for IUI. Moderate to severe OHSS risk of 0.9%/birth or 0.25% per cycle was related to IVF only and not IUI (Table 1). No maternal deaths were reported due to any complications but it can be argued the HFEA may not be fully informed as the death registry is not linked to the HFEA database. Terminations accounted for 0.81% of all total births (clinical pregnancy rates unavailable) in IVF and none in IUI. From 2012 to 2016 there were a total of 698 terminations evenly spread across this period. Medical reasons accounted for 73.6% of terminations with 22.4% of these being for Downs’s syndrome, and for the first time a 2.3% level of terminations for psychological and social reasons is revealed.
while a further 24.1% of terminations were for undisclosed reasons. For the first time, direct information on level of terminations after IVF (but no terminations in IUI) conception is indicated for social and psychological reasons adding a new dimension of debate in ART. It serves to underline the vital role for support and counselling before, during and after fertility treatment.

The economics of the fertility industry provides important insights as to how financial considerations are overriding evidence based medicine while suppressing the availability of low cost IUI. With regards to the financial information which can serve as important steers for patients and stakeholders in commissioning services emerge. The HFEA confirm the size of the IVF industry for 2016 to be worth around £320,000,000 in 2016, with a 61% growth in activity since 2007/08, revealing a mean tariff of £4699/cycle for IVF \(^{13}\). The wider annual estimate of the fertility industry is £500 million which includes other activities such as cryopreservation of gametes and embryos, and add-on techniques. The main real tariffs paid by NHS commissioning groups for IUI were £800 and £1,300 whereas for IVF £3,500-5,000 per cycle at the NHS level. The maternal and neonatal IVF risk burden of £115,082,017 representing 33-50% of the 2016 IVF market value is passed on to the NHS. The level of NHS IVF funding from 2012-2016 was at 42.5%, which is much higher than generally accepted, while a further 14.8% of IVF cycles were commissioned through private IVF practices. Private clinics are not public bodies and therefore are not accountable under the FOI Act. NHS funding for IUI in the UK was removed following the non-evidenced based NICE guidelines \(^2\) although some commissioning groups continue funding IUI. This clearly needs to be reversed with immediate effect.

The unique algorithm (Figure 1 and 2) reveals points of efficiencies and inefficiencies for IUI and IVF treatments and describes a spectrum of financial, economic and success relationships with each other. At baseline success rates for IUI (12.1% LBR) and IVF (27.3% LBR) (Fig 1), ICER favoured IUI over IVF by at least £13,663 to deliver 1 LB against the cheapest IVF tariff. When the realistic mean IVF tariff of £4699/cycle was considered mean IUI clinics could deliver a cost-effective benefit per LB of £42,558 (Fig1). Better performing IUI clinic at 15.6% LBR clinic could extend the cost savings to £76,257 per LB over mean IVF success of 27.3% LB and tariff of £4699. The cost savings to achieve 1 LB through improved IUI success over IVF are regarded as particularly high and beneficial to society. The algorithm defines the cost neutral point against mean IUI at 12.1% LBR, when IVF success reaches 32.58% (Fig 2) which can be extended to 42% LBR for IVF with IUI at 15.6% LBR using the same algorithm. This threshold can also be much higher for higher IVF tariff. For every 1% LB improvement of IUI, IVF success needs to improve by 2.7% LBR to achieve the same incremental cost benefit as IUI. In other words, IVF needs to work much harder than IUI to achieve benefits and suggests the need to invest in improving IUI success rates. These ICER cost efficiency values should persuade stakeholders and patients to choose IUI before IVF. IVF success rates have improved by 2% only to 27.3% LBR from 2012 to 2016 despite expensive non-evidenced based add-on techniques and treating potential IUI cases through IVF. On the reverse scale, cost effectiveness of IUI against lowest tariff IVF is maintained until the IUI success reaches 10.14% LBR (Fig 1). Below 10.14% LB, IUI loses its cost effectiveness against the lowest tariff IVF cycle. However, this lower IUI limit of 10.14% LBR will be even lower when considering higher tariff IVF (Fig 1) and which can be
extrapolated from Fig 1. Below these IUI low points practitioners need to re-evaluate their management, protocols or stop performing IUI.

Higher IVF success rate clinics are also associated with increased tariffs and MGP levels. A clinic with a 55% LBR success has around 28% MGP, and twice the normal UK MGP rate lose all benefits through increased tariffs ranging from £7,000-15,000 per cycle against mean IVF clinics. On tariff consideration alone, high performing IUI clinic is more cost effective than high performing IVF clinics where tariff factors alone erode any benefits. Based on success and tariffs only, IUI at 15.6% (tariff £800) vs. IVF at 27.3% (£4699) vs. IVF at 55% (£15,000) LBR, would cost the patients £5,128, £17,404 and £27,273 respectively to achieve 1 LB, notwithstanding the increasing risks for mother and babies along this sequence. The algorithm (Fig 1 and 2) also advises that the most expensive high performing IVF clinic at 55% LBR can match the mean IVF clinics at 27.3% LBR by dropping the tariff to £9572/cycle, provided these clinics can also reduce their MGP from 28% to 13.8% level. The financial analyses exclude the cost of OHSS, terminations and complication mainly for IVF, while there will be additional cost for drugs. Excluded also are the fees paid by IVF patients to cryopreserve embryos, back-up sperm or purchase add-on procedures.

Separate ICER calculations for high performing IUI (15.6% LBR, £800 tariff) against high performing IVF (55% LBR, £15,000) shows its £56,204 cheaper to gain 1 LB by IUI. Likewise, mid-performing IVF (27% LBR, £4699) against high performing IVF (55% LBR, £15,000) shows its £35,246 cheaper to gain 1 LB through mid-IVF clinics.

The algorithms allows detailed cross analyses of the practices and confirm IUI is superior to IVF to derive the best possible cost benefit to gain a child while minimising the risk to mother and babies if applicable. The second line option is for patients to choose a mid-performing IVF clinic paying attention to MGP levels. Evidenced based bodies have a duty of care to explicitly inform stakeholders when ICER is favourable, and in this case IUI is dominant over IVF.

The second major cost analyses relates to the MGP maternal and neonatal related cost burden which has remained invisible to date. For 2016, the IVF cost burden to the NHS was £115 million (£532 million over 2012-2016), against the IVF clinics turnover estimated between £340-538 million depending on the tariffs range £3,500 -5,000/per cycle cost considered. The HFEA mean cost estimate per cycle treatment for 2016 was £4699/cycle and a market worth of £320 million. In contrast the IUI market worth was £3.24-5.3 million using tariffs of £800-1300, against the negative cost impact of £2.94 million for 2016. It’s prudent to fund only essential IVF through modified eSET, to control the costs and minimising MGP.

Patients and stakeholders also need to consider intervention related risks and long term risks before making choices. IUI and IVF both have common underlying risks relating to the general health pathologies of subfertile couples and due to ovarian stimulation protocols. However, there appear long term added risks for babies from IVF, ICSI, embryo culture and freezing procedures. The added risks have been reported for singleton IVF babies and singletons after fetal reduction having pre-term weights, and large sized babies from frozen embryo procedures. Late onset diseases relating to increased risk of some cancers are being reported. In vitro embryo cultures and
exposures may affect later life developments along with any (epi) genetic modifications provide added risks or lead to higher imprinting disorders such as Beckwith–Wiedemann syndrome compared with naturally conceived children.

To summarise, this study has demonstrated that IUI has reduced risks of MGP, OHSS, fetal reduction or terminations. Success cannot to be considered in isolation of risks and cost. For every 1% LB improvement of IUI, expensive IVF needs to improve by 2.7% LBR to achieve the same incremental cost benefit as IUI. To produce 1 LB, IUI is more cost effective than IVF, yielding extraordinary cost and health safety benefits and potentially releasing funds to enable all deserving patients receive IVF. For international fertility healthcare commissioners, it is prudent to commission IUI first and encourage improving IUI success rates before undertaking IVF given the extraordinary cost effectiveness in delivering 1 baby.

In conclusion, this unique unfettered integrated analysis of success, risks and cost using a large regulated database defines the true relationship between IUI and IVF, and what it means for patients, stakeholders and the national budget. The question this study set out to decipher was what the success, risks and costs of IUI and IVF treatments were, as practiced. The analysis confirms IUI success is much closer to IVF than previously considered, is of lesser risks and more cost effective than IVF in delivering 1 LB. This report represents profound public interest information.

Footnotes

- Contributors: GB and RH framed the hypothesis, PR undertook the FOI requests, PH and KJ performed statistical analyses independently of each other, RA developed the financial models and algorithms. GB, RH (Professor), JH (Professor and Head of gynaecological department), PH, KJ, I.K, AI (Specialist IUI nurse), JEB (Professor of Healthcare Economics), AAH, EJ provided clinical information and critical analyses throughout. All authors helped prepare and reviewed the final manuscript.

- Funding: This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

- Competing interests: All authors have completed the ICMJE uniform disclosure forms at [www.icmje.org/coi_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: no support from any organisation for the submitted work.

- Ethical approval: Not required.

- Data sharing: All data are freely available on request and can be accessed from the UK HFEA regulatory body.

- The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

- Acknowledgments: We are grateful to the HFEA, NICE, Department of Health and Social Care (DH) and various Clinical Commissioning Groups (CCG), for providing information under FOI requests. Independent additional help was provided by private businessmen,
financial analysts, economist and accountants, especially for checking on financial calculations.

**Patient and Public Involvement:** No patient involved.

**References**


Table 1: UK IVF and IUI 2012-2016 outcomes

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<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
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<th>2012</th>
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<th>2016</th>
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<td>17,487</td>
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<td>11,739</td>
<td>82,8</td>
<td>73,6</td>
<td>67,4</td>
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<td>505</td>
<td>305</td>
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<td>14.16</td>
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<tr>
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<td>(% multiples per birth)</td>
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<td>572</td>
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<td>Total OHSS****</td>
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<td>165</td>
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<td>0.2</td>
<td>0.25</td>
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<td>Fetal Reduction</td>
<td>31</td>
<td>40</td>
<td>27</td>
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<td>159</td>
<td>Fetal Reduction</td>
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<td>0.15</td>
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<td>Termination</td>
<td>128</td>
<td>123</td>
<td>139</td>
<td>168</td>
<td>139</td>
<td>697</td>
<td>Termination</td>
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<td>Termination/tota l births %</td>
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<td>0.75</td>
<td>0.8</td>
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<td>47140</td>
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<tr>
<td>(% of all cycles)</td>
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<td>15.56</td>
<td>14.11</td>
<td>14.58</td>
<td>14.77</td>
<td>(% of all cycles)</td>
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<tr>
<td>(% of NHS funded cycles)</td>
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<td>38</td>
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< 5 suppressed for reasons of confidentiality

*Unusually high number (15) of triplets in 2013 coming from 6 clinics only

HFEA only require centres to report cases of severe/critical OHSS, or other critical episodes.
Fig 1 & 2: Economic and financial analyses of IUI versus IVF- direct cost effective analyses to deliver 1 LB based on actual success rates and tariffs for IUI and IVF (see Discussion)

Fig 1

Savings on IUI cycles to standard 27.3% IVF success rate

IUI success rate against IVF baseline rate of 27.3% LBR

- savings in IUI compared to IVF cycle (IUI lower cost-£800) for 1 birth
- savings in IUI compared to IVF cycle (IUI higher cost-£1300) for 1 birth
- savings in IUI compared to IVF cycle (HFEA mean - £4699) for 1 birth
- savings in IUI compared to IVF cycle (private clinic - £7000) for 1 birth
Fig 2

Additional cost for 1 extra birth in IVF compared to 12.1% IUI LBR

- Additional cost in IVF compared to IUI cycle lower cost (£800) for 1 birth
- Additional cost in IVF compared to IUI cycle higher cost (£1300) for 1 birth
- Additional cost in IVF compared to HFEA mean (£4699) for 1 birth
- Additional cost in IVF compared to private clinic (£7000) for 1 birth
A UK National Survey for patients and stakeholders: Outcomes of 319,105 IVF/ICSI and 30,669 IUI treatment cycles

This is a retrospective observational study of 319,105 IVF/ICSI and 30,669 IUI cycles performed between 2012 and 2016 in the UK. Direct cost for maternal and neonatal expenditure per LB was constructed using the Cost of Multiple Birth (COMBS) model, with inflation-adjusted pricing using Bank of England index-linked data. A second direct cost analysis evaluating the incremental cost effective ration (ICER) was modelled on the 2016 national mean (baseline) IVF and IUI success rates.

Results This largest comprehensive analysis integrating success, risks and costs at a national level shows IUI is safer and more cost effective than IVF treatment. IUI success is much closer to IVF than previously considered, while IVF remains a significant source of MGP. Uniquely, reliable levels of MGP, OHSS, fetal reductions and terminations associated with IVF are revealed. IUI is more cost effective in delivering 1 LB and this effectiveness is maintained against top-end IVF clinics, which lose residual benefits through increased MGP and tariffs. The huge IVF maternal and neonatal cost burden has remained invisible so far and is passed onto the NHS.

Conclusion IUI should be practiced before IVF. IUI success is much closer to IVF than previously considered, more cost effective in delivering 1 LB, cost efficient towards maternal and neonatal care, less risky for mothers and babies in terms of MGP, OHSS, fetal reduction and termination.
measurement assessment (measurement). Describe comparability of assessment methods if there is more than one group

Bias

Describe any efforts to address potential sources of bias

Page 2 – 2 Biased removed – Data collection by HFEA under FOI request removes selective data collection

Study size

Explain how the study size was arrived at

Page 2 – Not applicable. very large sized data set

Quantitative variables

Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why

Simple descriptive statistics only

Statistical methods

(a) Describe all statistical methods, including those used to control for confounding

(b) Describe any methods used to examine subgroups and interactions

(c) Explain how missing data were addressed

(d) If applicable, describe analytical methods taking account of sampling strategy

(e) Describe any sensitivity analyses

Simple descriptive statistics only (Page 4

Results

Participants

(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed

(b) Give reasons for non-participation at each stage

(c) Consider use of a flow diagram

Page 2 Largest dataset so far studied

Descriptive data

(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders

(b) Indicate number of participants with missing data for each variable of interest

Page 4-8

Outcome data

Report numbers of outcome events or summary measures

Page 4-8

Main results

(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included

(b) Report category boundaries when continuous variables were categorized

(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Tables 1 and Fig 1 and 2

Other analyses

Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

Financial cost analyses

Discussion

Key results

Summarise key results with reference to study objectives

Page 9-12

Limitations

Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias

Page 3

Interpretation

Give a cautious overall interpretation of results considering objectives, limitations,
The multiplicity of analyses, results from similar studies, and other relevant evidence should be discussed in the main text of the manuscript. This information can be found on page 6-8, 12-13.

### Generalisability

<table>
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<th>Discuss the generalisability (external validity) of the study results</th>
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**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

*Give information separately for exposed and unexposed groups.*

### Funding

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*Give information separately for exposed and unexposed groups.*
Observational retrospective study of UK national success, risks and costs for 319,105 IVF/ICSI and 30,669 IUI treatment cycles

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<td>Complete List of Authors:</td>
<td>Bahadur, Gulam; North Middlesex University Hospital NHS Trust, Homburg, Roy; Homerton Fertility Unit, Homerton University Hospital, Homerton Row, London E9 6SR, UK Bosmans, J; VU University Amsterdam Huirne, Judith; VU University Medical Center, Department of Obstetrics and Gynaecology Hinstridge, Peter; North Middlesex University Hospital NHS Trust Jayaprakasan, Kanna ; University Hospitals of Derby and Burton NHS Trust, Royal Derby Hospital, Derby. UK Racich, Paul; Oxford University Alam, Rakib; North Middlesex University Hospital NHS Trust Karapanos, Ioannis; North Middlesex University Hospital NHS Trust ILLAHIBUCCUS, Afeeza; North Middlesex University Hospital NHS Trust Al-Habib , Ansam; North Middlesex University Hospital NHS Trust Jauniaux, Eric; UCL, EGA Institute for Women Health</td>
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Observational retrospective study of UK national success, risks and costs for 319,105 IVF/ICSI and 30,669 IUI treatment cycles

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7EGA Institute for Womens Health, Faculty of Population Health Science, University College London, London, WC1E 6HX, UK

*Correspondence address. E-mail: bahadur.g@gmail.com

Abstract

Objective To compare success rates, associated risks and cost-effectiveness between IUI and IVF.

Design Retrospective observational study.

Setting The UK from 2012-2016

Participants Data from Human Fertilisation and Embryology Authority Freedom of Information (FOI) Request for 2012-2016 for in vitro fertilisation (IVF/ICSI) and intrauterine insemination (IUI) as practiced in 319,105 IVF/ICSI and 30669 IUI cycles. Direct-cost calculations for maternal and neonatal expenditure per live birth (LB) was constructed using the Cost of Multiple Birth (COMBS) model, with inflation-adjusted Bank of England index-linked data. A second direct-cost analysis evaluating the incremental cost-effective ratio (ICER) was modelled using the 2016 national mean (baseline) IVF and IUI success rates.

Outcome measures LB, risks from IVF and IUI, and costs to gain 1 LB

Results This largest comprehensive analysis integrating success, risks and costs at a national level shows IUI is safer and more cost effective than IVF treatment.

IVF LB/cycle success was significantly better than IUI at 26.96 % versus 11.49% (p<.001) but the IUI success is much closer to IVF at 2.35:1, than previously considered. IVF remains a significant source of multiple gestation pregnancy (MGP) compared to IUI(RR: 1.45 (1.31-1.60) p<0.001]) as was the rate of twins [RR: 1.58, p<0.001]).

In 2016, IVF maternal and neonatal cost was £115,082,017 compared to £2,940,196 for IUI and this MPG related perinatal cost is absorbed by the National Health Services (NHS). At baseline tariffs and success rates IUI was £42,558 cheaper than IVF to deliver 1LB with enhanced benefits with small improvements in IUI. Reliable levels of IVF related MGP, OHSS, fetal reductions and terminations are revealed.
**Conclusion** IUI success rates are much closer to IVF than previously reported, more cost-effective in delivering 1 LB, associated with lower risk of complications for maternal and neonatal complications. It is prudent to offer IUI before IVF nationally.

**Strengths and limitations of this study**

- Retrospective cohort study of one of the largest aggregate UK statutory national data on IVF/ICSI and IUI cycles.

- Data obtained from HFEA under FOI overcomes selection biases.

- Data reveals real-time and as actually practiced success rate, extent of risks of OHSS, fetal reduction, terminations, while revealing extent of higher order multiple births.

- Unique unfettered integrated analyses of success, risks and costs to achieve 1 LB from IUI or IVF procedures assists stakeholders and governments develop treatment policies to reduce risks and improve patient choices.

- Limitations stem from unavailability of associated clinical data such as diagnosis or stimulation or the segregation of IVF and ICSI data to go alongside the baseline data for IUI and IVF provided by the HFEA.

**Introduction**

There is limited comprehensive and direct comparison between intrauterine insemination (IUI) and in-vitro fertilisation (IVF) treatments at national level encompassing success, risk and cost.

Information on different assisted reproductive techniques (ART) success, risks, failures and costs can be challenging for patients, politicians and healthcare stakeholders paying for services. IVF success claims have an overbearing presence on social media and inpatient forums to such an extent that other ART such as IUI are relegated or dismissed outright. The HFEA website ¹ appears wholly negative towards IUI suggesting poor success, uncontrolled multiple births and a high cost of failure over several cycles.

The UK National Institute of Health and Care Excellence ² examined the effectiveness of 25mg clomiphene citrate with IUI against expectant management and found no differences, but then without comparative IUI and IVF evidence, recommended removing IUI altogether and replacing it with three cycles of IVF ²-³.

A recent systematic review and meta-analysis including 10 randomised controlled trials (RCTs) comparing IUI and IVF found no difference in safety and effectiveness between treatments ⁴. The overall quality of the evidence provided by RCTs has been low or very low for all comparisons ⁴. Subsequent well designed RCTs support IUI over IVF ⁵-⁸.
There are no large national data analyses. A European meta-analysis relying on voluntary data submission identified 1 million underreported cycles from 6 million cycles which would compromise interpretations of the data. Statutory National data analysis removes the selection bias of individual studies and the incompleteness of voluntary data submissions.

We aimed to compare the effectiveness of IUI with IVF as practiced in the UK over a 5-year period where full data was available. The hypothesis tested was that IUI would be associated with better outcomes than IVF in terms of pregnancy success rates, risk of complications and costs.

Methods

Study design and participants

This is a retrospective observational study of 319,105 IVF/ICSI and 30669 IUI cycles performed between 2012 and 2016 in the UK. DI cycles were excluded. Data were obtained from the UK-regulated HFEA database. The data was collected entirely by HFEA staff under FOI including LB per cycle, multiple births, OHSS, fetal reduction, terminations and level of government funded IVF cycles for IVF and IUI. Other clinic data was available on the HFEA website.

Direct cost for maternal and neonatal expenditure per LB was constructed using the COMBS model as previously described, with inflation-adjusted pricing using Bank of England index-linked data. The final figures were derived from the number of IUI and IVF cycles performed in 2016, against the level of MGP produced. Twin and triplet analyses allows for an individualised cost calculation for every birth component to be applied evenly and accurately for maternal and neonatal care based on the COMBS model.

A second direct cost analysis evaluating the ICER was modelled on the 2016 national mean (baseline) IVF and IUI success rates. An algorithm was developed to establish the relationships between IUI and IVF at prevailing baseline LBR and costs to determine cost effectiveness from clinics with variable success rates.

The relationship between IUI and IVF clinics with high LBR was considered alongside the standard performing clinics using the HFEA database and for IUI additional in-house (North Middlesex University Hospital, NMUH) data was available. The calculations were also performed using the mean 2016 IVF tariff. The common tariffs per treatment cycle for IUI at £800-£1300 and £3,500-5000 (HFEA mean £4699/cycle) were entered into our algorithm model, while IVF outliers for success and tariffs were considered separately.

Randomisation and masking

The very large data relates to actual and overall national practice and overrides RCT requirements for stratification or masking where small numbers are considered. RCTs are also associated with selected population and involve experimental design to control external factors.
Limitation of the FOI dataset is the absence of information on ovarian stimulation regimes, number of patients treated, mean number of treatment cycles per patient, cause of subfertility, extent of eSET, previous ART, oocyte retrieval complications, birth weight, sex ratios, gestational age and ectopic and molar pregnancies. Repeated FOI request could generate small differences in data given the enormity of the data gathering exercise. Unfactored also are the costs due to OHSS, fetal reduction, termination, sperm/embryo freezing, embryo culture, add on techniques and work absenteeism. There was no distinction between IVF and ICSI cycles. A general diagnosis for 2012-2016 of male infertility (37%); unexplained (32%); ovulatory disorder (13%); tubal disease (12%), endometriosis (6%) was provided for IVF/ICSI only.

Procedures

The procedures are fully described under methods section. The procedure of data collection was through FOI requests from the UK HFEA collecting information as part of its regulatory remit and for the purpose of issuing a licence to clinics to operate. There is therefore no scope for clinics to selectively submit or withhold their activities or outcome data. The HFEA provided a summary of the data in tabulated form which also restricts further interrogation of data or the manner in which statistics can be performed. The HFEA also provided details to reveal the nature of pregnancy terminations.

None of the authors could influence the data set or the manner in which data could further inclusion/exclusion choices, as this was handed over under FOI by the HFEA. No UK clinic could selectively submit data to the HFEA. Submission is a statutory obligation, resulting in revocation of the clinic licence for serious breaches.

Outcomes

The primary outcome was LB per cycle, MGP levels, OHSS, fetal reduction and terminations. The reasons for terminations were disclosed. The total cost of maternal and neonatal care through IUI and IVF for 2016 was calculated using actual 2016 figures derived from the COMBS model and inflation adjusted figures from the Bank of England data. ICER, to deliver 1 LB was obtained for real IUI and IVF activities and actual tariffs paid by patients. The percentage of IVF cycles was disclosed by the HFEA, and the level of funded treatments performed by NHS-funded private IVF clinics (which are not accountable under FOI laws).

Statistical analysis

The proportions with the standard error (SE) were calculated for the given outcome. The 95% CI was calculated as +/- 1.96 SE. Absolute and relative differences in risk were calculated, together with their SE. p values were calculated from the ratio of the measured absolute difference to the standard error, assuming variation to be normally distributed. Analysis was performed for main outcome measures such as LB rates, MGP rates, market worth of interventions against maternal and neonatal costs, and cost to achieve 1 LB and permutation thereof. Within IVF and IUI activity trends were calculated using Graphpad Prism software (version 8). For each exposure and outcome studied, relative risks were calculated using Medcalc software (https://www.medcalc.org/calc/relative_risk.php). For each comparison, the standard
error was calculated for the difference in absolute risk, and a two-tailed z-score calculated. 5% (p=0.05) was taken as the limit of significance.

Results

Data from the UK HFEA database between 2012-2016, showed an overall 10.4-fold increased use of IVF compared to IUI. The downward trend in IUI cycles was statistically significant R$^2$ of 0.89 (p<0.05) (Table 1), whereas there was a statistically significant increase in IVF cycle showing a significant slope R$^2$ of 0.99 (p<0.001) (Table 1).

There was a statistically significant improvement in LBR (live birth rate) for IVF between 2012 and 2016 [2012: 25.47% (25.12-25.82); 2016: 27.32% (26.98-27.65). Absolute difference: 1.84% (1.36 -2.33). RR: 1.07 (1.05-1.09) p<0.001]. The improvement from 25% to 27% LB/cycle for IVF remains small.

There was no change in IUI success over the same period [2012: 11.66% (10.93-12.39; 2016: 12.10% (11.09-12.10). The absolute difference was 0.43% (-0.81-1.67). RR: 1.04 (0.93-1.15) p=0.25 (Table 1). IVF had a significantly higher LB/cycle compared to IUI [IVF: 26.96% (26.81-27.12); IUI: 11.49% (11.13-11.85). Absolute difference: 15.47% (15.09-15.86). RR: 2.35 (2.27-2.42) p<0.001]. An additional birth will be achieved for every 6.5 IVF cycles compared to IUI (NNT=6.46) (Table 1).

The rate of MGP as a proportion of all births was significantly higher after IVF than IUI [IVF: 13.88% (13.65-14.11); IUI: 9.59% (8.62-10.56) with absolute difference: 4.29% (3.29-5.29). RR: 1.45 (1.31-1.60) p<0.001]. An additional multiple pregnancy will occur for every 23 IVF pregnancies compared to IUI (NNT = 23.31) (Table 1).

Data from 2012-2016 (Table 1) reveal other risks such as OHSS, fetal reduction and terminations and the level of government funded IVF cycles and additionally the level commissioned through private IVF clinics. As part of the risk factor association, reasons for terminations were additionally disclosed by the HFEA. Results from Table 1 is discussed in detail.

Financial calculation

Two types of financial analyses are included(a) the national maternal and neonatal care cost burden and (b) ICER, to deliver 1 LB per cycle (Fig 1 and 2).

Size of maternal and neonatal cost: Based on HFEA 2012-2016 figures 1 LB from IUI is made up of singleton: twin: triplet in the components 91.25: 7.90: 0.85 respectively, whereas for IVF the singleton component is reduced in the proportion 86.21: 13.65: 0.14. Twin and triplet figures were number of sets, rather than individual babies. For 2016, maternal and neonatal, adapted from COMBS model and index link adjusted for 2016, the cost (£) per birth events factoring the singleton, twin and triplet cost was £4945, £13618, £48300 respectively. Associated maternal and neonatal cost for one IUI and IVF baby was £6000.406525 and £6186.538342 respectively.

Financial size of the 2016 UK IVF and IUI industry against the MGP risk cost burden for the NHS

The IVF maternal and neonatal cost for 2016 was £115,082,017 against the IVF market value of £238,346,500 to £340,495,000 for 2016. In contrast, for IUI the maternal and neonatal risk burden from IUI was £2,940,196 against the IUI market value of £3,240,800 -5,266,300. The maternal and neonatal risk burden due to IVF is 39-fold higher than IUI, against a 10.4-fold greater IVF activity over IUI. The size of maternal and neonatal care for the UK from IVF or IUI could not be confirmed by The Department of Health and Social Care’s (FOI Response FOI-1160477).
To understand the relationships between high LBR IUI and IVF clinics, data from North Middlesex University Hospital (NMUH) IUI at £800 tariff was utilised. Between 2014-18: 672 cycles, 364 women, 119 pregnancies, 2 twins; PR/cycle 17.7%/cycle; PR/woman 32.7%/woman; LB/Woman 28.7%/woman; LB/cycle 15.60%; 2 twins, no severe to moderate OHSS reportable to the HFEA, but 7 cases of mild-moderate OHSS not requiring hospitalisation; 63% of all cycles performed using consecutive ejaculation, hMG stimulated with strict cancellation policy for >=3 follicles or OHSS. Against this, typical higher undisclosed IVF clinic results showed 55% LB/cycle and 30% MGP rates from the HFEA database, and which also had typical IVF tariff of £7,000-15,000/cycle. Both sets of data were placed in perspective against standard IVF clinics where the mean success rate for 2016 was 27% LB/cycle and with a mean tariff of £4699.

Table 1: UK IVF and IUI 2012-2016 outcomes

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<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>Total</th>
<th>IUI</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>Total</th>
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<th>p value</th>
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<td>&lt;5*</td>
<td>Quadruptplet birth</td>
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* < 5 (1-5) suppressed for reasons of confidentiality

** Unusually high number (15) of triplets in 2013 coming from 6 clinics only

*** The triplet numbers for 2012 and 2015 was withheld by HFEA to prevent the true numbers of quadruplets to become available. This figure is adjusted to incorporate 1-5 quadruplets as the final birth numbers is available. The RR remains unchanged with 1 or 5 added numbers.

HFEA only require centres to report cases of severe/critical OHSS, or other critical episodes.
Discussion

This data adds to previously published studies showing better LBR following IVF than with IUI but this difference is much smaller than previously reported. Our study has also identified new data on the use of IVF and IUI in the UK which should have a direct impact in management strategies of couples presenting with infertility. Data summary provided by the HFEA has also allowed us to perform descriptive comparisons and trends, but limits the use of complex statistics. This is advantageous as alternative interpretations of the data become impossible, thereby removing interest biases. No sample size calculation was required to determine the power at a significance level of 0.05.

During the period of our study, IVF was associated with a significantly (p<0.001) higher risk of MGP than IUI. IVF is also associated with higher risks of OHSS and need for fetal reduction and pregnancy terminations which were not found after IUI. We found that over 2012 to 2016, there was 10.4-fold increase in the use of IVF over IUI with a significant (p<0.05) increase in IVF cycles and a corresponding declining in IUI cycles (Table 1). This increased IVF activity cannot be justified on the basis of evidence-based data, since there are no comparative IVF versus IUI data. The increase in the number of IVF and decline in IUI cycles (Table 1) coincide with the 2013 NICE guidelines recommendation against the use of IUI as the primary therapeutic line for infertile couples. This erroneous recommendation was based poor IUI outcomes compared to expectant management with no data on IVF and yet recommended IVF practice instead of IUI. Our data show a small increased but significant (p<0.05) LBR following IVF from 25% to 27% during that period following the NICE recommendation.

The baseline IUI: IVF success rates (Table 1) to deliver 1 LB was 2.35:1, which was much narrower than the RCT reported of 3:1 for IUI: IVF. Therefore, a small improvement in IUI LBR from 12.1% to 15.6% LBR narrows this difference to 1.73:1, IUI: IVF cycles, with a highly favourable cost benefit for IUI over IVF. When considering IVF as a denominator it is important to emphasise that 3.7 IVF cycles are actually required to achieve a 100% theoretical LB. Overall, we found 8.69 IUI cycles at 12.1% LBR or 6.4 cycle for a 15.6% LBR IUI NMUH clinic are needed to theoretically achieve 100% LB. Despite the focus on IUI against IVF, the relationship between ordinary and high success IVF clinics seems curiously avoided. Mean-IVF clinics (27% LBR, MGP 15%) against as high performing IVF clinic (55% LBR, MGP 30%) have a 2.04:1 relationship but higher IVF clinics have riskier (2.2:1) outcomes for mother and baby.

Factoring tariffs alone, IUI is cheaper than IVF while also delivering lesser risks and perinatal complications for both mothers and babies. Higher IVF success clinics lose any benefits through increased tariffs and doubled MGP levels against IUI and against standard performing IVF clinics. The actual cost benefits are displayed in Fig 1 and Fig 2 which study the ICER to deliver 1 LB at various success rates and tariffs. Against prevailing tariffs IUI always has lower overall costs than IVF in commissioning treatment to achieve 1 LB. Patients should be informed that IUI success is closer to IVF but without the added risks to mothers and babies, the cost burden to the health care system of which are excessive for IVF.
A recent RCT shows that after 3-4 years unexplained infertility randomised for three cycles of IUI (CC) or expectant management 5 a three-fold improvement in outcome in LBR from 31% and 9% is seen. IUI LB/cycle probabilities ranged from 21.4% to 5.1% dependent on age, cycle number and previous parity, with a MGP of 5.4% 18. IUI was also effective on LBR (OR 1.95 (1.10 to 3.44) (95% CI)) when compared with intercourse or expectant management in a stimulated cycle 19. Currently in most clinics, IUI suited cases are now receiving IVF treatments or are further aided with non-evidenced based add-on techniques 19. IUI success rates appear to face downward pressures from IVF clinics by managing difficult cases through IUI 20.

So far no reliable national figures exist for the levels of different risks for patients undergoing IVF and IUI to help them towards a journey of making informed decisions or to help clinicians counsel their patients. With this large database, the MGP rate as a proportion of all births was significantly higher following IVF than following IUI (RR: 1.45 (1.31-1.60) p<0.001). This fact contradicts popular belief that IUI being the source of uncontrolled MGP. The rate of twins was also significantly higher following IVF [RR: 1.58, p<0.001]. There was 0.2% fetal reductions performed for IVF and none for IUI. Moderate to severe OHSS risk of 0.9%/birth or 0.25% per cycle was related to IVF only and not IUI (Table 1). No maternal deaths were reported due to any complications but it can be argued the HFEA may not be fully informed as the death registry is not linked to the HFEA database. Terminations accounted for 0.81% of all total births (clinical pregnancy rates unavailable) in IVF and none in IUI. From 2012 to 2016 there were a total of 698 terminations evenly spread across this period. Medical reasons accounted for 73.6% of terminations with 22.4% of these being for Downs’s syndrome, and for the first time a 2.3% level of terminations for psychological and social reasons is revealed, while a further 24.1% of terminations were for undisclosed reasons. For the first time, direct information on level of terminations after IVF (but no terminations in IUI) conception is indicated for social and psychological reasons adding a new dimension of debate in ART. It serves to underline the vital role for support and counselling before, during and after fertility treatment.

The economics of the fertility industry provides important insights as to how financial considerations are overriding evidence-based medicine while suppressing the availability of low cost IUI. With regards to the financial information which can serve as important steers for patients and stakeholders in commissioning services emerge. The HFEA confirm the size of the IVF industry for 2016 to be worth around £320, 000,000 in 2016, with a 61% growth in activity since 2007/08, revealing a mean tariff of £4699/cycle for IVF 13. The wider annual estimate of the fertility industry is £500 million which includes other activities such as cryopreservation of gametes and embryos, and add-on techniques. The main real tariffs paid by NHS commissioning groups for IUI were £800 and £1,300 whereas for IVF £3,500-5,000 per cycle at the NHS level. The maternal and neonatal IVF risk burden of £115,082,017 representing 33-50% of the 2016 IVF market value is passed on to the NHS. The level of NHS IVF funding from 2012-2016 was at 42.5%, which is much higher than generally accepted, while a further 14.8% of IVF cycles were commissioned through private IVF practices. Private clinics are not public bodies and therefore are not accountable under the FOI Act. NHS funding for IUI in the UK was removed following the non-evidenced based NICE guidelines 2 although some commissioning groups continue funding IUI. This clearly needs to be reversed with immediate effect.
The unique algorithm (Figure 1 and 2) reveals points of efficiencies and inefficiencies for IUI and IVF treatments and describes a spectrum of financial, economic and success relationships with each other. At baseline success rates for IUI (12.1% LBR) and IVF (27.3% LBR) (Fig 1), ICER favoured IUI over IVF by at least £13,663 to deliver 1 LB against the cheapest IVF tariff. When the realistic mean IVF tariff of £4699/cycle was considered mean IUI clinics could deliver a cost-effective benefit per LB of £42,558 (Fig1). Better performing IUI clinic at 15.6% LBR clinic could extend the cost savings to £76,257 per LB over mean IVF success of 27.3% LB and tariff of £4699. The cost savings to achieve 1 LB through improved IUI success over IVF are regarded as particularly high and beneficial to society. The algorithm defines the cost neutral point against mean IUI at 12.1% LBR, when IVF success reaches 32.58% (Fig 2) which can be extended to 42% LBR for IVF with IUI at 15.6% LBR using the same algorithm. This threshold can also be much higher for higher IVF tariff. For every 1% LB improvement of IUI, IVF success needs to improve by 2.7% LBR to achieve the same incremental cost benefit as IUI. In other words, IVF needs to work much harder than IUI to achieve benefits and suggests the need to invest in improving IUI success rates. These ICER cost efficiency values should persuade stakeholders and patients to choose IUI before IVF. IVF success rates have improved by 2% only to 27.3% LBR from 2012 to 2016 despite expensive non-evidenced based add-on techniques and treating potential IUI cases through IVF. On the reverse scale, cost effectiveness of IUI against lowest tariff IVF is maintained until the IUI success reaches 10.14% LBR (Fig 1). Below 10.14% LB, IUI loses its cost effectiveness against the lowest tariff IVF cycle. However, this lower IUI limit of 10.14% LBR will be even lower when considering higher tariff IVF (Fig 1) and which can be extrapolated from Fig 1. Below these IUI low points practitioners need to re-evaluate their management, protocols or stop performing IUI.

Higher IVF success rate clinics are also associated with increased tariffs and MGP levels. A clinic with a 55% LBR success has around 28% MGP, and twice the normal UK MGP rate lose all benefits through increased tariffs ranging from £7,000-15,000 per cycle against mean IVF clinics. On tariff consideration alone, high performing IUI clinic is more cost effective than high performing IVF clinics where tariff factors alone erode any benefits. Based on success and tariffs only, IUI at 15.6% (tariff £800) vs. IVF at 27.3% (£4699) vs. IVF at 55% (£15,000) LBR, would cost the patients £5,128, £17,404 and £27,273 respectively to achieve 1 LB, notwithstanding the increasing risks for mother and babies along this sequence. The algorithm (Fig 1 and 2) also advises that the most expensive high performing IVF clinic at 55% LBR can match the mean IVF clinics at 27.3% LBR by dropping the tariff to £9572/cycle, provided these clinics can also reduce their MGP from 28% to 13.8% level. The financial analyses exclude the cost of OHSS, terminations and complication mainly for IVF, while there will be additional cost for drugs. Excluded also are the fees paid by IVF patients to cryopreserve embryos, back-up sperm or purchase add-on procedures.

Separate ICER calculations for high performing IUI (15.6% LBR, £800 tariff) against high performing IVF (55% LBR, £15,000) shows its £56,204 cheaper to gain 1 LB by IUI. Likewise, mid-performing IVF (27% LBR, £4699) against high performing IVF (55% LBR, £15,000) shows its £35,246 cheaper to gain 1 LB through mid-IVF clinics. The algorithms allow detailed cross analyses of the practices and confirm IUI is superior to IVF to derive the best possible cost benefit to gain a child while minimising the risk to
mother and babies if applicable. The second line option is for patients to choose a mid-performing IVF clinic paying attention to MGP levels. Evidenced based bodies have a duty of care to explicitly inform stakeholders when ICER is favourable, and in this case IUI is dominant over IVF. Previous cost effective studies have been performed against extremely poor IUI results, while relying on optimal IVF in local settings to persuade purchasers to fund more IVF cycles instead of IUI.

The second major cost analyses relates to the MGP maternal and neonatal related cost burden which has remained invisible to date. For 2016, the IVF cost burden to the NHS was £115 million (£532 million over 2012-2016), against the IVF clinics turnover estimated between £340-538 million depending on the tariffs range £3,500 -5,000/per cycle cost considered. The HFEA mean cost estimate per cycle treatment for 2016 was £4699/cycle and a market worth of £320 million. In contrast the IUI market worth was £3.24-5.3 million using tariffs of £800-1300, against the negative cost impact of £2.94 million for 2016. It’s prudent to fund only essential IVF such as bilateral tubal blockages and severe male factor infertility as a priority before considering IUI failed cases through modified eSET in order to control costs while minimising MGP.

Patients and stakeholders also need to consider intervention related risks and long term risks before making choices. IUI and IVF both have common underlying risks relating to the general health pathologies of subfertile couples and due to ovarian stimulation protocols. However, there appear long term added risks for babies from IVF, ICSI, embryo culture and freezing procedures. The added risks have been reported for singleton IVF babies and singletons after fetal reduction having pre-term weights, and large sized babies from frozen embryo procedures. Late onset diseases relating to increased risk of some cancers are being reported. In vitro embryo cultures and exposures may affect later life developments along with any (epi) genetic modifications provide added risks or lead to higher imprinting disorders such as Beckwith-Wiedemann syndrome compared with naturally conceived children. This is a dynamic and evolving area of research.

In conclusion, IUI LBRs are much closer to IVF than previously described. IUI is associated with lesser risks to mothers and babies and more cost effective than IVF in delivering 1 LB against current tariffs. IUI always has lower overall costs than IVF in commissioning treatment to achieve 1 LB. The cost burden to the health care system is excessive for IVF. This unfettered, uniquely integrated analysis of success, risks and cost provide important information to healthcare stakeholders and governments to develop effective fertility treatment policies.
Contributors: GB and RH framed the hypothesis, PR undertook the FOI requests, PH and KJ performed statistical analyses independently of each other, RA developed the financial models and algorithms. GB, RH (Professor), JH (Professor and Head of gynaecological department), PH, KJ, I.K, AI (Specialist IUI nurse), JEB (Professor of Healthcare Economics), AAH, EJ provided clinical information and critical analyses throughout. All authors helped prepare and reviewed the final manuscript.

Funding: This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests: All authors have completed the ICMJE uniform disclosure forms at [www.icmje.org/coi_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: no support from any organisation for the submitted work.

Ethical approval: Not required.


Acknowledgments: We are grateful to the HFEA, NICE, Department of Health and Social Care (DH) and various Clinical Commissioning Groups (CCG), for providing information under FOI requests. Independent additional help was provided by private businessmen, financial analysts, economist and accountants, especially for checking on financial calculations.

Patient and Public Involvement: No patient involved.

References


17. Tjon-Kon-Fat RI, Bensdorp AJ, and Bossuyt PMM. Is IVF—served two different ways—more cost-effective than IUI with controlled ovarian hyperstimulation? Hum Reprod. 2015; 10: pp. 2331-2339


22. Pashayan N, Lyratzopoulos G and Mathur R. Cost-effectiveness of primary offer of IVF vs. primary offer of IUI followed by IVF (for IUI failures) in couples with unexplained or mild male factor subfertility. BMC Health Services Research 2006, 6:80
doi:10.1186/1472-6963-6-80


Fig 1

Savings on IUI cycles to standard 27.3% IVF success rate

IUI success rate against IVF baseline rate of 27.3% LBR

- blue line: savings in IUI compared to IVF cycle (IUI lower cost-£800) for 1 birth
- red line: savings in IUI compared to IVF cycle (IUI higher cost-£1300) for 1 birth
- green line: savings in IUI compared to IVF cycle (HFEA mean - £4699) for 1 birth
- purple line: savings in IUI compared to IVF cycle (private clinic - £7000) for 1 birth

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
Fig 2

Additional cost for 1 extra birth in IVF compared to 12.1% IUI LBR

- Additional cost in IVF compared to IUI cycle lower cost (£800) for 1 birth
- Additional cost in IVF compared to IUI cycle higher cost (£1300) for 1 birth
- Additional cost in IVF compared to HFEA mean (£4699) for 1 birth
- Additional cost in IVF compared to private clinic (£5000) for 1 birth
STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

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<thead>
<tr>
<th>Item No</th>
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<tr>
<td><strong>Title and abstract</strong></td>
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<tr>
<td>(a) Indicate the study’s design with a commonly used term in the title or the abstract</td>
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<tr>
<td>A UK National Survey for patients and stakeholders: Outcomes of 319,105 IVF/ICSI and 30,669 IUI treatment cycles</td>
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<td>(b) Provide in the abstract an informative and balanced summary of what was done and what was found</td>
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<td>This is a retrospective observational study of 319,105 IVF/ICSI and 30669 IUI cycles performed between 2012 and 2016 in the UK. Direct cost for maternal and neonatal expenditure per LB was constructed using the Cost of Multiple Birth (COMBS) model, with inflation-adjusted pricing using Bank of England index-linked data. A second direct cost analysis evaluating the incremental cost effective ration (ICER) was modelled on the 2016 national mean (baseline) IVF and IUI success rates.</td>
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**Results** This largest comprehensive analysis integrating success, risks and costs at a national level shows IUI is safer and more cost effective than IVF treatment. IUI success is much closer to IVF than previously considered, while IVF remains a significant source of MGP. Uniquely, reliable levels of MGP, OHSS, fetal reductions and terminations associated with IVF are revealed. IUI is more cost effective in delivering 1 LB and this effectiveness is maintained against top-end IVF clinics, which lose residual benefits through increased MGP and tariffs. The huge IVF maternal and neonatal cost burden has remained invisible so far and is passed onto the NHS.

**Conclusion** IUI should be practiced before IVF. IUI success is much closer to IVF than previously considered, more cost effective in delivering 1 LB, cost efficient towards maternal and neonatal care, less risky for mothers and babies in terms of MGP, OHSS, fetal reduction and termination.

**Introduction**

| Background/rationale | 2 |
| Explain the scientific background and rationale for the investigation being reported | Page 1-2 of submitted manuscript |

| Objectives | 3 |
| State specific objectives, including any prespecified hypotheses | Start of page 1 – paragraph relating to Abstract |

**Methods**

| Study design | 4 |
| Present key elements of study design early in the paper | Page 1 and 2 |

| Setting | 5 |
| Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | Page 1 and 2 |

| Participants | 6 |
| (a) Give the eligibility criteria, and the sources and methods of selection of participants | Page 1and 3 |

| Variables | 7 |
| Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | Page 2 and 3 |

<p>| Data sources/ | 8* |
| For each variable of interest, give sources of data and details of methods of |</p>
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<td>Quantitative variables</td>
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multiplicity of analyses, results from similar studies, and other relevant evidence

**Generalisability**

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**Other information**

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*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.
Observational retrospective study of UK national success, risks and costs for 319,105 IVF/ICSI and 30,669 IUI treatment cycles

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Observational retrospective study of UK national success, risks and costs for 319,105 IVF/ICSI and 30,669 IUI treatment cycles

Gulam Bahadur1, *D. Phil(Oxon), Roy Homburg2 FRCOG, Judith E. Bosmans3 PhD, Judith Huirne4 PhD, MD, Peter Hinstridge5 MA, MBBS, MRCOG, Kannay Jayaprakasan6 MD, MRCOG, PhD, Paul Racich6 M.Lit (Oxon), MBA Economics and Finance, Rakib Alam7 ACMA, CGMA, CIMA, MRes Accounting with Finance, Ioannis Karapanos8 MSc., Afeeza Illahibuccus1 MB.CHB, FRCOG, DFFP, Eric Jauniaux7 MD, PhD, FRCOG

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Abstract

Objective To compare success rates, associated risks and cost-effectiveness between IUI and IVF.

Design Retrospective observational study.

Setting The UK from 2012-2016

Participants Data from Human Fertilisation and Embryology Authority Freedom of Information (FOI) Request for 2012-2016 for in vitro fertilisation (IVF/ICSI) and intrauterine insemination (IUI) as practiced in 319,105 IVF/ICSI and 30669 IUI cycles.

Direct-cost calculations for maternal and neonatal expenditure per live birth (LB) was constructed using the Cost of Multiple Birth (COMBS) model, with inflation-adjusted Bank of England index-linked data. A second direct-cost analysis evaluating the incremental cost-effective ratio (ICER) was modelled using the 2016 national mean (baseline) IVF and IUI success rates.

Outcome measures LB, risks from IVF and IUI, and costs to gain 1 LB

Results This largest comprehensive analysis integrating success, risks and costs at a national level shows IUI is safer and more cost effective than IVF treatment.

IVF LB/cycle success was significantly better than IUI at 26.96 % versus 11.49% (p<.001) but the IUI success is much closer to IVF at 2.35:1, than previously considered. IVF remains a significant source of multiple gestation pregnancy (MGP) compared to IUI(RR: 1.45 (1.31-1.60) p<0.001) as was the rate of twins [RR: 1.58, p<0.001]).

In 2016, IVF maternal and neonatal cost was £115,082,017 compared to £2,940,196 for IUI and this MPG related perinatal cost is absorbed by the National Health Services (NHS). At baseline tariffs and success rates IUI was £42,558 cheaper than IVF to deliver 1LB with enhanced benefits with small improvements in IUI. Reliable levels of IVF related MGP, OHSS, fetal reductions and terminations are revealed.
Conclusion IUI success rates are much closer to IVF than previously reported, more cost-effective in delivering 1 LB, associated with lower risk of complications for maternal and neonatal complications. It is prudent to offer IUI before IVF nationally.

Strengths and limitations of this study

- Largest aggregate UK statutory national data on IVF/ICSI and IUI treatment cycles from HFEA gained under FOI overcomes selection biases and ensures a high degree of applicability of the study results.

- Study uniquely describes comparative treatment outcomes, multiple birth risks, cost implications, including cost to achieve a live birth and of neonatal costs.

- Data reveals extent of other risks such as OHSS, fetal reduction; pregnancy terminations and the level of higher order multiple births.

- Retrospective and observational study.

- Limitations stem from unavailability of associated clinical data such as diagnosis or stimulation methods, distinction of IVF and ICSI cycles, fresh or frozen IVF cycles to go alongside the baseline IUI data.

Introduction

There is limited comprehensive and direct comparison between intrauterine insemination (IUI) and in-vitro fertilisation (IVF) treatments at national level encompassing success, risk and cost.

Information on different assisted reproductive techniques (ART) success, risks, failures and costs can be challenging for patients, politicians and healthcare stakeholders paying for services. IVF success claims have an overbearing presence on social media and in-patient forums to such an extent that other ART such as IUI are relegated or dismissed outright. The HFEA website \(^1\) appears wholly negative towards IUI suggesting poor success, uncontrolled multiple births and a high cost of failure over several cycles.

The UK National Institute of Health and Care Excellence \(^2\) examined the effectiveness of 25mg clomiphene citrate with IUI against expectant management and found no differences, but then without comparative IUI and IVF evidence, recommended removing IUI altogether and replacing it with three cycles of IVF \(^2-3\).

A recent systematic review and meta-analysis including 10 randomised controlled trials (RCTs) comparing IUI and IVF found no difference in safety and effectiveness between treatments \(^4\). The overall quality of the evidence provided by RCTs has been low or very low for all comparisons \(^4\). Subsequent well designed RCTs support IUI over IVF \(^5-8\).
There are no large national data analyses. A European meta-analysis relying on voluntary data submission identified 1 million underreported cycles from 6 million cycles which would compromise interpretations of the data. Statutory National data analysis removes the selection bias of individual studies and the incompleteness of voluntary data submissions.

We aimed to compare the effectiveness of IUI with IVF as practiced in the UK over a 5-year period where full data was available. The hypothesis tested was that IUI would be associated with better outcomes than IVF in terms of pregnancy success rates, risk of complications and costs.

**Methods**

**Study design and participants**

This is a retrospective observational study of 319,105 IVF/ICSI and 30669 IUI cycles performed between 2012 and 2016 in the UK. DI cycles were excluded. Data were obtained from the UK-regulated HFEA database. The data was collected entirely by HFEA staff under FOI including LB per cycle, multiple births, OHSS, fetal reduction, terminations and level of government funded IVF cycles for IVF and IUI. Other clinic data was available on the HFEA website.

Direct cost for maternal and neonatal expenditure per LB was constructed using the COMBS model as previously described, with inflation-adjusted pricing using Bank of England index-linked data. The final figures were derived from the number of IUI and IVF cycles performed in 2016, against the level of MGP produced. Twin and triplet analyses allows for an individualised cost calculation for every birth component to be applied evenly and accurately for maternal and neonatal care based on the COMBS model.

A second direct cost analysis evaluating the ICER was modelled on the 2016 national mean (baseline) IVF and IUI success rates. An algorithm was developed to establish the relationships between IUI and IVF at prevailing baseline LBR and costs to determine cost effectiveness from clinics with variable success rates.

The relationship between IUI and IVF clinics with high LBR was considered alongside the standard performing clinics using the HFEA database and for IUI additional in-house (North Middlesex University Hospital, NMUH) data was available. The calculations were also performed using the mean 2016 IVF tariff. The common tariffs per treatment cycle for IUI at £800-£1300 and £3,500-5000 (HFEA mean £4699/cycle) were entered into our algorithm model, while IVF outliers for success and tariffs were considered separately.

**Randomisation and masking**

The very large data relates to actual and overall national practice and overrides RCT requirements for stratification or masking where small numbers are considered. RCTs are also associated with selected population and involve experimental design to control external factors.
Limitation of the UK FOI dataset is the absence of information on ovarian stimulation regimes, number of patients treated, mean number of treatment cycles per patient, cause of subfertility, age of patient, use of fresh or frozen IVF cycles, the potential benefit and cost of transferring cryopreserved embryo in subsequent cycles, extent of eSET, previous ART, oocyte retrieval complications, birth weight, sex ratios, gestational age and ectopic and molar pregnancies. Repeated FOI request could generate small differences in data given the enormity of the data gathering exercise. Unfactored also are the costs due to OHSS, fetal reduction, termination, sperm/embryo freezing, embryo culture, add on techniques and work absenteeism. There was no distinction between IVF and ICSI cycles.

A general diagnosis for 2012-2016 of male infertility (37%); unexplained (32%); ovulatory disorder (13%); tubal disease (12%), endometriosis (6%) was provided for IVF/ICSI only.

Procedures

The procedures are fully described under methods section. The procedure of data collection was through FOI requests from the UK HFEA collecting information as part of its regulatory remit and for the purpose of issuing a licence to clinics to operate. There is therefore no scope for clinics to selectively submit or withhold their activities or outcome data. The HFEA provided a summary of the data in tabulated form which also restricts further interrogation of data or the manner in which statistics can be performed. The HFEA also provided details to reveal the nature of pregnancy terminations. None of the authors could influence the data set or the manner in which data could further inclusion/exclusion choices, as this was handed over under FOI by the HFEA. No UK clinic could selectively submit data to the HFEA. Submission is a statutory obligation, resulting in revocation of the clinic licence for serious breaches.

Outcomes

The primary outcome was LB per cycle, MGP levels, OHSS, fetal reduction and terminations. The reasons for terminations were disclosed. The total cost of maternal and neonatal care through IUI and IVF for 2016 was calculated using actual 2016 figures derived from the COMBS model and inflation adjusted figures from the Bank of England data. ICER, to deliver 1 LB was obtained for real IUI and IVF activities and actual tariffs paid by patients. The percentage of IVF cycles was disclosed by the HFEA, and the level of funded treatments performed by NHS-funded private IVF clinics (which are not accountable under FOI laws).

Statistical analysis

The proportions with the standard error (SE) were calculated for the given outcome. The 95% CI was calculated as +/- 1.96 SE. Absolute and relative differences in risk were calculated, together with their SE. p values were calculated from the ratio of the measured absolute difference to the standard error, assuming variation to be normally distributed. Analysis was performed for main outcome measures such as LB rates, MGP rates, market worth of interventions against maternal and neonatal costs, and cost to achieve 1 LB and permutation thereof. Within IVF and IUI activity trends were calculated using Graphpad Prism software (version 8). For each exposure and outcome
studied, relative risks were calculated using Medcalc software (https://www.medcalc.org/calc/relative_risk.php). For each comparison, the standard error was calculated for the difference in absolute risk, and a two-tailed z-score calculated. 5% (p=0.05) was taken as the limit of significance.

Results

Data from the UK HFEA database between 2012-2016, showed an overall 10.4-fold increased use of IVF compared to IUI. The downward trend in IUI cycles was statistically significant $R^2$ of 0.89 ($p<0.05$) (Table 1), whereas there was a statistically significant increase in IVF cycle showing a significant slope $R^2$ of 0.99 ($p<0.001$) (Table 1).

There was a statistically significant improvement in LBR (live birth rate) for IVF between 2012 and 2016 [2012: 25.47% (25.12-25.82); 2016: 27.32% (26.98-27.65). Absolute difference: 1.84% (1.36-2.33). RR: 1.07 (1.05-1.09) $p<0.001$]. The improvement from 25% to 27% LB/cycle for IVF remains small.

There was no change in IUI success over the same period [2012: 11.66% (10.93-12.39; 2016: 12.10% (11.09-12.10). The absolute difference was 0.43% (-0.81-1.67). RR: 1.04 (0.93-1.15) $p=0.25$ (Table 1). IVF had a significantly higher LB/cycle compared to IUI [IVF: 26.96% (26.81-27.12); IUI: 11.49% (11.13-11.85). Absolute difference: 15.47% (15.09-15.86). RR: 2.35 (2.27-2.42) $p<0.001$]. An additional birth will be achieved for every 6.5 IVF cycles compared to IUI (NNT=6.46) (Table 1).

The rate of MGP as a proportion of all births was significantly higher after IVF than IUI [IVF: 13.88% (13.65-14.11); IUI: 9.59% (8.62-10.56) with absolute difference: 4.29% (3.29-5.29). RR: 1.45 (1.31-1.60) $p<0.001$]. An additional multiple pregnancy will occur for every 23 IVF pregnancies compared to IUI (NNT = 23.31) (Table 1).

Data from 2012-2016 (Table 1) reveal other risks such as OHSS, fetal reduction and terminations and the level of government funded IVF cycles and additionally the level commissioned through private IVF clinics. As part of the risk factor association, reasons for terminations were additionally disclosed by the HFEA. Results from Table 1 is discussed in detail.

Financial calculation

Two types of financial analyses are included (a) the national maternal and neonatal care cost burden and (b) ICER, to deliver 1 LB per cycle (Fig 1 and 2).

Size of maternal and neonatal cost: Based on HFEA 2012-2016 figures 1 LB from IUI is made up of singleton: twin: triplet in the components 91.25: 7.90: 0.85 respectively, whereas for IVF the singleton component is reduced in the proportion 86.21: 13.65: 0.14. Twin and triplet figures were number of sets, rather than individual babies. For 2016, maternal and neonatal, adapted from COMBS model and index link adjusted for 2016, the cost (£) per birth events factoring the singleton, twin and triplet cost was £4945, £13618, £48300 respectively. Associated maternal and neonatal cost for one IUI and IVF baby was £6000.406525 and £6186.538342 respectively.

Financial size of the 2016 UK IVF and IUI industry against the MGP risk cost burden for the NHS

The IVF maternal and neonatal cost for 2016 was £115,082,017 against the IVF market value of £238,346,500 to £340,495,000 for 2016. In contrast, for IUI the maternal and neonatal risk burden from IUI was £2,940,196 against the IUI market value of £3,240,800 -5,266,300. The maternal and neonatal risk burden due to IVF is 39-fold higher than IUI, against a 10.4-fold greater IVF activity over IUI. The size of maternal
and neonatal care for the UK from IVF or IUI could not be confirmed by The Department of Health and Social Care’s (FOI Response FOI-1160477).

To understand the relationships between high LBR IUI and IVF clinics, data from North Middlesex University Hospital (NMUH) IUI at £800 tariff was utilised. Between 2014-18: 672 cycles, 364 women, 119 pregnancies, 2 twins; PR/cycle 17.7%/cycle; PR/woman 32.7%/woman; LB/Woman 28.7%/woman; LB/cycle 15.60%; 2 twins, no severe to moderate OHSS reportable to the HFEA, but 7 cases of mild-moderate OHSS not requiring hospitalisation; 63% of all cycles performed using consecutive ejaculation, hMG stimulated with strict cancellation policy for >=3 follicles or OHSS. Against this, typical higher undisclosed IVF clinic results showed 55% LB/cycle and 30% MGP rates from the HFEA database, and which also had typical IVF tariff of £7,000-15,000/cycle. Both sets of data were placed in perspective against standard IVF clinics where the mean success rate for 2016 was 27% LB/cycle and with a mean tariff of £4699.

Table 1: UK IVF and IUI 2012-2016 outcomes

<table>
<thead>
<tr>
<th>IVF</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>Total</th>
<th>IUI</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>Total</th>
<th>RR (IVF vs IUI)</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number cycles</td>
<td>60, 236</td>
<td>61, 848</td>
<td>63, 542</td>
<td>65, 380</td>
<td>68, 099</td>
<td>319, 105</td>
<td>Total number cycles</td>
<td>74, 784</td>
<td>794, 437</td>
<td>63, 47</td>
<td>48, 49</td>
<td>40, 51</td>
<td>30, 669</td>
<td>RR (IVF vs IUI)</td>
<td>95% CI</td>
<td>p value</td>
</tr>
<tr>
<td>Total births</td>
<td>15, 343</td>
<td>16, 441</td>
<td>17, 487</td>
<td>18, 172</td>
<td>18, 602</td>
<td>86, 045</td>
<td>Total births</td>
<td>87, 284</td>
<td>859, 741</td>
<td>71, 625</td>
<td>58, 714</td>
<td>49, 089</td>
<td>3, 524</td>
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<tr>
<td>(% Births per cycle)</td>
<td>25.47</td>
<td>26.58</td>
<td>27.52</td>
<td>27.79</td>
<td>27.32</td>
<td>26.96</td>
<td>(% Births per cycle)</td>
<td>11.66</td>
<td>10.81</td>
<td>11.28</td>
<td>12.11</td>
<td>12.10</td>
<td>11.49</td>
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<td>Singletons</td>
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<td>13, 937</td>
<td>14, 974</td>
<td>15, 827</td>
<td>16, 575</td>
<td>74, 099</td>
<td>Singletons</td>
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<td>771, 649</td>
<td>64, 539</td>
<td>44, 449</td>
<td>3, 187</td>
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<td>(% singletons per birth)</td>
<td>83.33</td>
<td>84.77</td>
<td>85.63</td>
<td>87.10</td>
<td>89.10</td>
<td>86.12</td>
<td>(% singletons per birth)</td>
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<td>91.82</td>
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<td>(% twins per birth)</td>
<td>16.34</td>
<td>14.96</td>
<td>14.16</td>
<td>12.66</td>
<td>10.73</td>
<td>13.64</td>
<td>9.40</td>
<td>8.50</td>
<td>9.36</td>
<td>8.14</td>
<td>7.86</td>
<td>8.65</td>
<td>1.5</td>
<td>1.4</td>
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<td><strong>Triplet birth</strong>*</td>
<td>(50)</td>
<td>45</td>
<td>37</td>
<td>(44)</td>
<td>31</td>
<td>207</td>
<td>6</td>
<td>15</td>
<td>0</td>
<td>&lt;5*</td>
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<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.1</td>
<td>0.2</td>
<td>0.1</td>
<td>1.7</td>
<td>1.22</td>
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<td>&lt;5*</td>
<td>0</td>
<td>&lt;5*</td>
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<td>(% multiples per birth)</td>
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<td>10.90</td>
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<td>10</td>
<td>91</td>
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<td><strong>Total OHSS</strong></td>
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<td>18</td>
<td>13</td>
<td>16</td>
<td>13</td>
<td>781</td>
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<td><strong>OHSS/Birth %</strong></td>
<td>1.1</td>
<td>1.1</td>
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<td>0.9</td>
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<td><strong>OHSS/cycle %</strong></td>
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<td>0.3</td>
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<th>Fetal Reduction</th>
<th>31</th>
<th>40</th>
<th>27</th>
<th>31</th>
<th>30</th>
<th>159</th>
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<td>0.2</td>
<td>0.1</td>
<td>0.1</td>
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<td>Fetal Reduction/total births %</td>
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<td>8</td>
<td>13</td>
<td>9</td>
<td>16</td>
<td>8</td>
<td>697</td>
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<td>Termination/total births %</td>
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<td>0.7</td>
<td>0.8</td>
<td>0.9</td>
<td>0.7</td>
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<td>Termination/total births %</td>
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<td>NHS funded cycles</td>
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<td>48</td>
<td>26,</td>
<td>01</td>
<td>27,</td>
<td>10</td>
<td>28,</td>
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<td>4</td>
<td>2</td>
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<tr>
<td>% NHS funded cycles</td>
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<td>65</td>
<td>42.</td>
<td>06</td>
<td>42.</td>
<td>66</td>
<td>43.</td>
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<td>42.</td>
<td>9</td>
<td>42.</td>
<td>68</td>
<td>42.</td>
<td>49</td>
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<tr>
<td>NHS funded through private IVF clinics</td>
<td>8.2</td>
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<td>9.8</td>
<td>56</td>
<td>9.8</td>
<td>89</td>
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<td>9.9</td>
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<td>471</td>
<td>40</td>
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<td>% of all cycles</td>
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<td>67</td>
<td>15.</td>
<td>94</td>
<td>15.</td>
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<td>14.</td>
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<td>14.</td>
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<tr>
<td>% of NHS funded cycles</td>
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<td>38</td>
<td>36</td>
<td>33</td>
<td>33</td>
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* < 5 (1-5) suppressed for reasons of confidentiality

**Unusually high number (15) of triplets in 2013 coming from 6 clinics only

*** The triplet numbers for 2012 and 2015 was withheld by HFEA to prevent the true numbers of quadruplets to become available. This figure is adjusted to incorporate 1-5 quadruplets as the final birth numbers is available. The RR remains unchanged with 1 or 5 added numbers.

HFEA only require centres to report cases of severe/critical OHSS, or other critical episodes.
Discussion

This data adds to previously published studies\textsuperscript{5-8,15-17} showing better LBR following IVF than with IUI but this difference is much smaller than previously reported. Our study has also identified new data on the use of IVF and IUI in the UK which should have a direct impact in management strategies of couples presenting with infertility. Data summary provided by the HFEA has also allowed us to perform descriptive comparisons and trends, but limits the use of complex statistics. This is advantageous as alternative interpretations of the data become impossible, thereby removing interest biases. No sample size calculation was required to determine the power at a significance level of 0.05.

During the period of our study, IVF was associated with a significantly (p<0.001) higher risk of MGP than IUI. IVF is also associated with higher risks of OHSS and need for fetal reduction and pregnancy terminations which were not found after IUI. We found that over 2012 to 2016, there was 10.4-fold increase in the use of IVF over IUI with a significant (p<0.05) increase in IVF cycles and a corresponding declining in IUI cycles (Table 1). This increased IVF activity cannot be justified on the basis of evidence-based data, since there are no comparative IVF versus IUI data\textsuperscript{3}. The increase in the number of IVF and decline in IUI cycles (Table 1) coincide with the 2013 NICE guidelines\textsuperscript{3} recommendation against the use of IUI as the primary therapeutic line for infertile couples. This erroneous recommendation was based poor IUI outcomes compared to expectant management with no data on IVF and yet recommended IVF practice instead of IUI\textsuperscript{3}. Our data show a small increased but significant (p<0.05) LBR following IVF from 25% to 27% during that period following the NICE recommendation.

The baseline IUI: IVF success rates (Table 1) to deliver 1 LB was 2.35:1, which was much narrower than the RCT reported of 3:1 for IUI: IVF\textsuperscript{5-8,15-17}. Therefore, a small improvement in IUI LBR from 12.1% to 15.6% LBR narrows this difference to 1.73:1, IUI: IVF cycles, with a highly favourable cost benefit for IUI over IVF. When considering IVF as a denominator it is important to emphasise that 3.7 IVF cycles are actually required to achieve a 100% theoretical LB. Overall, we found 8.69 IUI cycles at 12.1% LBR or 6.4 cycle for a 15.6% LBR IUI NMUH clinic are needed to theoretically achieve 100% LB. Despite the focus on IUI against IVF, the relationship between ordinary and high success IVF clinics seems curiously avoided. Mean-IVF clinics (27% LBR, MGP 15%) against as high performing IVF clinic (55% LBR, MGP 30%) have a 2.04:1 relationship but higher IVF clinics have riskier (2.2:1) outcomes for mother and baby.

Factoring tariffs alone, IUI is cheaper than IVF while also delivering lesser risks and perinatal complications for both mothers and babies. Higher IVF success clinics lose any benefits through increased tariffs and doubled MGP levels against IUI and against standard performing IVF clinics. The actual cost benefits are displayed in Fig 1 and Fig 2 which study the ICER to deliver 1 LB at various success rates and tariffs. Against prevailing tariffs IUI always has lower overall costs than IVF in commissioning treatment to achieve 1 LB. Patients should be informed that IUI success is closer to IVF but without the added risks to mothers and babies, the cost burden to the health care system of which are excessive for IVF.
A recent RCT shows that after 3-4 years unexplained infertility randomised for three cycles of IUI (CC) or expectant management 5 a three-fold improvement in outcome in LBR from 31% and 9% is seen. IUI LB/cycle probabilities ranged from 21.4% to 5.1% dependent on age, cycle number and previous parity, with a MGP of 5.4% 18. IUI was also effective on LBR (OR 1.95 (1.10 to 3.44) (95% CI)) when compared with intercourse or expectant management in a stimulated cycle 19. Currently in most clinics, IUI suited cases are now receiving IVF treatments or are further aided with non-evidenced based add-on techniques 19. IUI success rates appear to face downward pressures from IVF clinics by managing difficult cases through IUI 20.

So far no reliable national figures exist for the levels of different risks for patients undergoing IVF and IUI to help them towards a journey of making informed decisions or to help clinicians counsel their patients. With this large database, the MGP rate as a proportion of all births was significantly higher following IVF than following IUI (RR: 1.45 (1.31-1.60) p<0.001). This fact contradicts popular belief that IUI being the source of uncontrolled MGP. The rate of twins was also significantly higher following IVF [RR: 1.58, p<0.001] . There was 0.2% fetal reductions performed for IVF and none for IUI. Moderate to severe OHSS risk of 0.9%/birth or 0.25% per cycle was related to IVF only and not IUI (Table 1). No maternal deaths were reported due to any complications but it can be argued the HFEA may not be fully informed as the death registry is not linked to the HFEA database. Terminations accounted for 0.81% of all total births (clinical pregnancy rates unavailable) in IVF and none in IUI. From 2012 to 2016 there were a total of 698 terminations evenly spread across this period. Medical reasons accounted for 73.6% of terminations with 22.4% of these being for Down’s syndrome, and for the first time a 2.3% level of terminations for psychological and social reasons is revealed, while a further 24.1% of terminations were for undisclosed reasons. For the first time, direct information on level of terminations after IVF (but no terminations in IUI) conception is indicated for social and psychological reasons adding a new dimension of debate in ART. It serves to underline the vital role for support and counselling before, during and after fertility treatment.

The economics of the fertility industry provides important insights as to how financial considerations are overriding evidence-based medicine while suppressing the availability of low cost IUI. With regards to the financial information which can serve as important steers for patients and stakeholders in commissioning services emerge. The HFEA confirm the size of the IVF industry for 2016 to be worth around £320, 000,000 in £4699/cycle for IVF 13. The wider annual estimate of the fertility industry is £500 million which includes other activities such as cryopreservation of gametes and embryos, and add-on techniques. The main real tariffs paid by NHS commissioning groups for IUI were £800 and £1,300 whereas for IVF £3,500-5,000 per cycle at the NHS level. The maternal and neonatal IVF risk burden of £115,082,017 representing 33-50% of the 2016 IVF market value is passed on to the NHS. The level of NHS IVF funding from 2012-2016 was at 42.5%, which is much higher than generally accepted, while a further 14.8% of IVF cycles were commissioned through private IVF practices. Private clinics are not public bodies and therefore are not accountable under the FOI Act. NHS funding for IUI in the UK was removed following the non-evidenced based NICE guidelines 2 although some commissioning groups continue funding IUI. This clearly needs to be reversed with immediate effect.
The unique algorithm (Figure 1 and 2) reveals points of efficiencies and inefficiencies for IUI and IVF treatments and describes a spectrum of financial, economic and success relationships with each other. At baseline success rates for IUI (12.1% LBR) and IVF (27.3% LBR) (Fig 1), ICER favoured IUI over IVF by at least £13,663 to deliver 1 LB against the cheapest IVF tariff. When the realistic mean IVF tariff of £4699/cycle was considered mean IUI clinics could deliver a cost-effective benefit per LB of £42,558 (Fig 1). Better performing IUI clinic at 15.6% LBR clinic could extend the cost savings to £76,257 per LB over mean IVF success of 27.3% LBR and tariff of £4699. The cost savings to achieve 1 LB through improved IUI success over IVF are regarded as particularly high and beneficial to society. The algorithm defines the cost neutral point against mean IUI at 12.1% LBR, when IVF success reaches 32.58% (Fig 2) which can be extended to 42% LBR for IVF with IUI at 15.6% LBR using the same algorithm. This threshold can also be much higher for higher IVF tariff. For every 1% LB improvement of IUI, IVF success needs to improve by 2.7% LBR to achieve the same incremental cost benefit as IUI. In other words, IVF needs to work much harder than IUI to achieve benefits and suggests the need to invest in improving IUI success rates. These ICER cost efficiency values should persuade stakeholders and patients to choose IUI before IVF. IVF success rates have improved by 2% only to 27.3% LBR from 2012 to 2016 despite expensive non-evidenced based add-on techniques and treating potential IUI cases through IVF. On the reverse scale, cost effectiveness of IUI against lowest tariff IVF is maintained until the IUI success reaches 10.14% LBR (Fig 1). Below 10.14% LB, IUI loses its cost effectiveness against the lowest tariff IVF cycle. However, this lower IUI limit of 10.14% LBR will be even lower when considering higher tariff IVF (Fig 1) and which can be extrapolated from Fig 1. Below these IUI low points practitioners need to re-evaluate their management, protocols or stop performing IUI.

Higher IVF success rate clinics are also associated with increased tariffs and MGP levels. A clinic with a 55% LBR success has around 28% MGP, and twice the normal UK MGP rate lose all benefits through increased tariffs ranging from £7,000-15,000 per cycle against mean IVF clinics. On tariff consideration alone, high performing IUI clinic is more cost effective than high performing IVF clinics where tariff factors alone erode any benefits. Based on success and tariffs only, IUI at 15.6% (tariff £800) vs. IVF at 27.3% (£4699) vs. IVF at 55% (£15,000) LBR, would cost the patients £5,128, £17,404 and £27,273 respectively to achieve 1 LB, notwithstanding the increasing risks for mother and babies along this sequence. The algorithm (Fig 1 and 2) also advises that the most expensive high performing IVF clinic at 55% LBR can match the mean IVF clinics at 27.3% LBR by dropping the tariff to £9572/cycle, provided these clinics can also reduce their MGP from 28% to 13.8% level. The financial analyses exclude the cost of OHSS, terminations and complication mainly for IVF, while there will be additional cost for drugs. Excluded also are the fees paid by IVF patients to cryopreserve embryos, back-up sperm or purchase add-on procedures.

Separate ICER calculations for high performing IUI (15.6% LBR, £800 tariff) against high performing IVF (55% LBR, £15,000) shows its £56,204 cheaper to gain 1 LB by IUI. Likewise, mid-performing IVF (27% LBR, £4699) against high performing IVF (55% LBR, £15,000) shows its £35,246 cheaper to gain 1 LB through mid-IVF clinics. The algorithms allow detailed cross analyses of the practices and confirm IUI is superior to IVF to derive the best possible cost benefit to gain a child while minimising the risk to
mother and babies if applicable. The second line option is for patients to choose a mid-performing IVF clinic paying attention to MGP levels. Evidenced based bodies have a duty of care to explicitly inform stakeholders when ICER is favourable, and in this case IUI is dominant over IVF. Previous cost effective studies have been performed against extremely poor IUI results, while relying on optimal IVF in local settings to persuade purchasers to fund more IVF cycles instead of IUI.

The second major cost analyses relates to the MGP maternal and neonatal related cost burden which has remained invisible to date. For 2016, the IVF cost burden to the NHS was £115 million (£532 million over 2012-2016), against the IVF clinics turnover estimated between £340-538 million depending on the tariffs range £3,500 -5,000/per cycle cost considered. The HFEA mean cost estimate per cycle treatment for 2016 was £4699/cycle and a market worth of £320 million. In contrast the IUI market worth was £3.24-5.3 million using tariffs of £800-1300, against the negative cost impact of £2.94 million for 2016. It’s prudent to fund only essential IVF such as bilateral tubal blockages and severe male factor infertility as a priority before considering IUI failed cases through modified eSET in order to control costs while minimising MGP.

There are some critical limitations to the current study and the main one being it was an observational and retrospective in nature, with the main concern being selection bias of data collection. However, the unique nature of having gained the treatment cycles data under FOI from the UK regulatory body, the potential for selection bias is minimised. The data does not reveal the baseline characteristics and treatment details of patients such as age, cause, type and duration of subfertility, prognostic indicators like ovarian reserve status, stimulation protocols, fresh or frozen IVF cycles, the distinction between IVF or ICSI or the number of cycles of treatment each patient has undergone to be able to comment on the cumulative success rates. Further limitation of the study relates to non-random selection of IUI or IVF treatment in this study with good prognosis patients may have been selected for IUI or IVF as first choice. Contrastingly, some poor prognosis patients may have chosen lesser invasive IUI treatment as the only option and some have had IVF cycle cancellation with subsequent rescue IUI cycles, both of which may potentially bias IUI and IVF success rates. Specific patient pathologies such as severe male factor infertility or bilateral tubal blockages will obviously necessitate IVF procedures creating a degree of selection bias but this cannot be revealed from our data analyses. However, it is important to recognise that by analysing aggregate national UK data for the entire subfertile population rather than a sample of the population, the risks of selection and treatment biases are somewhat mitigated and potentially allowing a high degree of data generalisability. Stakeholders in other countries should review their practices, risks and costs of assisted reproductive procedures based on our UK experience.

Patients and stakeholders also need to consider intervention related risks and long-term risks before making choices. IUI and IVF both have common underlying risks relating to the general health pathologies of subfertile couples and due to ovarian stimulation protocols. However, there appear long term added risks for babies from IVF, ICSI, embryo culture and freezing procedures. The added risks have been reported for singleton IVF babies and singletons after fetal reduction having pre-term weights, and large sized babies from frozen embryo procedures. Late onset diseases relating to increased risk of some cancers are being reported. In vitro embryo cultures and
exposures may affect later life developments along with any (epi) genetic modifications provide added risks or lead to higher imprinting disorders such as Beckwith–Wiedemann syndrome compared with naturally conceived children. This is a dynamic and evolving area of research.

In conclusion, IUI LBRs are much closer to IVF than previously described. IUI is associated with lesser risks to mothers and babies and more cost effective than IVF in delivering 1 LB against current tariffs. IUI always has lower overall costs than IVF in commissioning treatment to achieve 1 LB. The cost burden to the health care system is excessive for IVF. Some selection bias cannot be excluded to the retrospective design and the data should be interpreted with caution. However, this unfettered, uniquely integrated analysis of success, risks and cost provide important information to healthcare stakeholders and governments to develop effective fertility treatment policies.

Footnotes

Contributors: GB and RH framed the hypothesis, PR undertook the FOI requests, PH and KJ performed statistical analyses independently of each other, RA developed the financial models and algorithms). GB, RH (Professor), JH (Professor and Head of gynaecological department), PH, KJ, I.K, AI (Specialist IUI nurse), JEB (Professor of Healthcare Economics), AAH, EJ provided clinical information and critical analyses throughout. All authors helped prepare and reviewed the final manuscript.

Funding: This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests: All authors have completed the ICMJE uniform disclosure forms at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work.

Ethical approval: Not required.

Data sharing statement: Source data are available from the UK HFEA regulatory body. https://www.hfea.gov.uk/choose-a-clinic/clinic-search/ https://www.hfea.gov.uk/about-us/publications/research-and-data/. FOI information gained is as presented within the manuscript.
Acknowledgments: We are grateful to the HFEA, NICE, Department of Health and Social Care (DH) and various Clinical Commissioning Groups (CCG), for providing information under FOI requests. Independent additional help was provided by private businessmen, financial analysts, economist and accountants, especially for checking on financial calculations.

Patient and Public Involvement: No patient involved.

References


17. Tjon-Kon-Fat RI, Bensdorp AJ, and Bossuyt PMM. Is IVF—served two different ways—more cost-effective than IUI with controlled ovarian hyperstimulation? Hum Reprod 2015; 10: pp. 2331-2339


Fig 1

Savings on IUI cycles to standard 27.3% IVF success rate

IUI success rate against IVF baseline rate of 27.3% LBR

- Savings in IUI compared to IVF cycle (IUI lower cost - £800) for 1 birth
- Savings in IUI compared to IVF cycle (IUI higher cost - £1300) for 1 birth
- Savings in IUI compared to IVF cycle (HFEA mean - £4699) for 1 birth
- Savings in IUI compared to IVF cycle (private clinic - £7000) for 1 birth
Fig 2

Additional cost for 1 extra birth in IVF compared to 12.1% IUI LBR

- Blue line: additional cost in IVF compared to IUI cycle lower cost (£800) for 1 birth
- Red line: additional cost in IVF compared to IUI cycle higher cost (£1300) for 1 birth
- Green line: additional cost in IVF compared to HFEA mean (£4699) for 1 birth
- Purple line: additional cost in IVF compared to private clinic (£6000) for 1 birth

IVF success rate against IUI baseline rate of 12.1% LBR
### STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

<table>
<thead>
<tr>
<th>Item No</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>1</td>
<td><em>(a)</em> Indicate the study’s design with a commonly used term in the title or the abstract</td>
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<tr>
<td>2</td>
<td><em>(b)</em> Provide in the abstract an informative and balanced summary of what was done and what was found</td>
</tr>
</tbody>
</table>

**Title and abstract**

A UK National Survey for patients and stakeholders: Outcomes of 319,105 IVF/ICSI and 30,669 IUI treatment cycles

This is a retrospective observational study of 319,105 IVF/ICSI and 30669 IUI cycles performed between 2012 and 2016 in the UK. Direct cost for maternal and neonatal expenditure per LB was constructed using the Cost of Multiple Birth (COMBS) model, with inflation-adjusted pricing using Bank of England index-linked data. A second direct cost analysis evaluating the incremental cost effective ration (ICER) was modelled on the 2016 national mean (baseline) IVF and IUI success rates.

**Results**

This largest comprehensive analysis integrating success, risks and costs at a national level shows IUI is safer and more cost effective than IVF treatment. IUI success is much closer to IVF than previously considered, while IVF remains a significant source of MGP. Uniquely, reliable levels of MGP, OHSS, fetal reductions and terminations associated with IVF are revealed. IUI is more cost effective in delivering 1 LB and this effectiveness is maintained against top-end IVF clinics, which lose residual benefits through increased MGP and tariffs. The huge IVF maternal and neonatal cost burden has remained invisible so far and is passed onto the NHS.

**Conclusion**

IUI should be practiced before IVF. IUI success is much closer to IVF than previously considered, more cost effective in delivering 1 LB, cost efficient towards maternal and neonatal care, less risky for mothers and babies in terms of MGP, OHSS, fetal reduction and termination.

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**Introduction**

**Background/rationale**

Explain the scientific background and rationale for the investigation being reported

Page 1-2 of submitted manuscript

**Objectives**

State specific objectives, including any prespecified hypotheses

Start of page 1 – paragraph relating to Abstract

**Methods**

**Study design**

Present key elements of study design early in the paper

Page 1 and 2

**Setting**

Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection

Page 1 and 2

**Participants**

*(a)* Give the eligibility criteria, and the sources and methods of selection of participants

Page 1 and 3

**Variables**

Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable

Page 2 and 3

**Data sources/**

For each variable of interest, give sources of data and details of methods of
measurement assessment (measurement). Describe comparability of assessment methods if there is more than one group

Page 2 and 3

Bias 9 Describe any efforts to address potential sources of bias
Page 2 – 2 Biased removed – Data collection by HFEA under FOI request removes selective data collection

Study size 10 Explain how the study size was arrived at
Page 2 – Not applicable. very large sized data set

Quantitative variables 11 Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Simple descriptive statistics only

Statistical methods 12 (a) Describe all statistical methods, including those used to control for confounding
(b) Describe any methods used to examine subgroups and interactions
(c) Explain how missing data were addressed
(d) If applicable, describe analytical methods taking account of sampling strategy
(e) Describe any sensitivity analyses
Simple descriptive statistics only (Page 4)

Results

Participants 13* (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
(b) Give reasons for non-participation at each stage
(c) Consider use of a flow diagram
Page 2 Largest dataset so far studied

Descriptive data 14* (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
(b) Indicate number of participants with missing data for each variable of interest
Page 4-8

Outcome data 15* Report numbers of outcome events or summary measures
Page 4-8

Main results 16 (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
(b) Report category boundaries when continuous variables were categorized
(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Tables 1 and Fig 1 and 2

Other analyses 17 Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Financial cost analyses

Discussion

Key results 18 Summarise key results with reference to study objectives
Page 9-12

Limitations 19 Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Page 3

Interpretation 20 Give a cautious overall interpretation of results considering objectives, limitations,
multiplicity of analyses, results from similar studies, and other relevant evidence

Generalisability 21 Discuss the generalisability (external validity) of the study results
Page 6-8, 12-13

Other information

Funding 22 Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based
No funding was received for this study

*Give information separately for exposed and unexposed groups.