OPTUMHealth Education

OHS Clinical Educational Series

Optimizing Infertility Treatment

Alexander M Dlugi, MD, MBA

National Medical Director, Fertility Solutions | Optum Health Solutions

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Disclosure Information

- No pertinent financial disclosures or conflicts of interest

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Introduction of Faculty

- Alexander M Dlugi, MD, MBA
- National Medical Director, Fertility Solutions
- Optum since March 2011
- Board Certified in Obstetrics and Gynecology and Reproductive Endocrinology

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Optum Fertility Solutions

- 23 UM Nurses
- 21 CM Nurses
- 1 Team Lead
- 2 Nurse Managers
- 1 Part-time Social Worker
- 2 Board Certified Reproductive Endocrinologist Medical Directors
- Product
- Contracting

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Objectives

- Review the basics of infertility evaluation and treatment
- Address cost effective treatment
- Understand the means to minimize multiple gestations following infertility treatment
- Define the merits of and issues surrounding elective single embryo transfer

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Definition of Infertility

- A disease (an interruption, cessation, or disorder of body functions, systems, or organs) of the reproductive tract which prevents the conception of a child or the ability to carry a pregnancy to delivery. It is defined by the failure to achieve a successful pregnancy after 12 months or more of appropriate, timed unprotected intercourse or Therapeutic Donor Insemination. Earlier evaluation and treatment may be justified based on medical history and physical findings and is warranted after 6 months for women aged 35 years or older.
- The presence of an identified infertility factor should allow for immediate treatment, obviating the need for the waiting period to meet the definition of infertility when an individual is actively attempting to achieve a conception.
- Recurrent pregnancy loss is a disease distinct from infertility, defined by two or more failed pregnancies. When the cause is unknown, each pregnancy loss merits careful review to determine whether specific evaluation may be appropriate. (ASRM)

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Etiology of Infertility

Overall

- Female 40%
- Male 40%
- Couple 20%

Female

- Ovarian Function 40%
- Tubal/Peritoneal 40%
- Uterine 10%
- Cervical 10%

Male

- Sperm Abnormalities
  - Decreased count, motility, morphology
- Sexual Dysfunction

Unexplained/Undetermined

- Absence of an apparent diagnosis
  - Fertilization Errors
  - Implantation Failure
  - Oocyte abnormalities
  - Embryo abnormalities
  - Unknown

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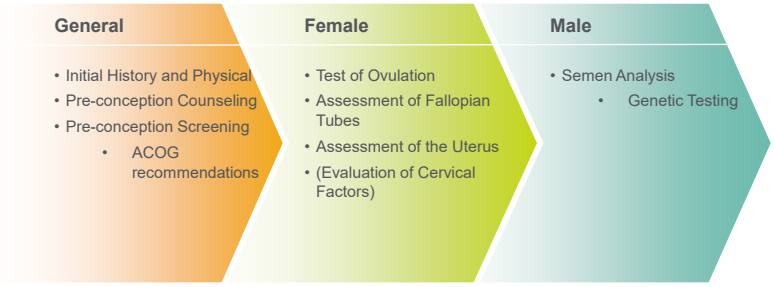
The Infertility Evaluation



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Infertility Treatment- The Old Paradigm

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Infertility Treatments – the old model

Diagnosis	Treatment Option 1	Treatment Option 2	Treatment Option 3

• Ovulatory Factor	• Ovulation Induction with Clomiphene
	  • 6 or more cycles
		• Ovulation Induction with Gonadotropins
		  • 6 or more cycles
			• IVF as a last resort

• Tubal/Peritoneal Factor	• Surgery	• Ovarian stimulation (clomiphene first, then gonadotropins) following surgery with or without intrauterine insemination (IUI)	• Additional surgery • IVF as a last resort
• Uterine Factor	• Surgery	• Ovarian stimulation (clomiphene first, then gonadotropins) following surgery with or without intrauterine insemination	• Additional surgery or IVF

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Infertility Treatments – the old model

Diagnosis	Treatment Option 1	Treatment Option 2	Treatment Option 3
• Cervical Factor	• Intrauterine insemination – natural cycle	Ovarian stimulation (clomiphene first, then gonadotropins) with intrauterine insemination	• Laparoscopy if not successful. • IVF as a last resort
• Male Factor	• Intrauterine insemination – natural cycle	• Ovarian stimulation (clomiphene first, then gonadotropins) with intrauterine insemination	• Laparoscopy if not successful • IVF as a last resort
• Unexplained Infertility	• Intrauterine insemination-natural cycle	• Ovarian stimulation (clomiphene first, then gonadotropins) with intrauterine insemination	• Laparoscopy if not successful • IVF as a last resort

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Outcomes

- The success of treatment outcome with Ovarian Stimulation/IUI is dependent upon:
  - Age
    - <35 10-15%
    - 35-40 7-10%
    - >40 <7%
  - Diagnosis
    - Male Factor 2-7%
    - Unexplained 10%
- Ovarian Stimulation /IUI often requires multiple cycles
  - 90% of conceptions should occur within 3-4 cycles
- Ovarian Stimulation /IUI is associated with a 25% chance of a multiple gestation and is the source of most high order (triplet or greater) pregnancies

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Outcomes- Unexplained Infertility

- Pregnancy Rate/Cycle
  - No treatment 1.3-4.1%
  - IUI 3.8%
  - Ovarian Stimulation /IUI 5-20%
    - Aggressive therapy yields higher rate but with a significant risk for a multiple gestation
  - IVF 20-60%
    - Depending upon age and other factors

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Infertility Treatments – the contemporary model

Diagnosis	Treatment Option 1	Treatment Option 2	Treatment Option 3
• Ovulatory Factor	• Ovulation Induction with Clomiphene • 6 ovulatory cycles	• Ovulation Induction with Gonadotropins if no response to clomiphene • 4 cycles	• IVF
• Tubal/Peritoneal Factor	• IVF		
• Uterine Factor	• Surgery	• IVF	

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Infertility Treatments – the contemporary model

Diagnosis	Treatment Option 1	Treatment Option 2	Treatment Option 3
• Cervical Factor	• Intrauterine insemination – only for sexual dysfunction or surgical trauma to the cervix	• IVF	
• Male Factor	• 3 cycles of oral medication/IUI for mild to moderate male factor	IVF with ICSI	
• Unexplained Infertility	• 3 cycles of oral medications/IUI	• IVF	

A Direct Move to IVF is appropriate

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Ovarian Stimulation with or without IUI

- Accounts for 22.8% of the national multiple birth cohort

Outcome characteristics of representative prospective, randomized trials of SO/IUI using high-dose (≥150 IU) GTs (FSH/hMG).

First author (reference)	Year	Cycles (n)	Participants (n)	Pregnancy/cycle (%)	Twin IUP (%)	High-order IUP (%)
Dodson (24)	1991	78	78	19.2	0	6.7
Nulsen (25)	1993	294	119	12.2	18.2	0
Sengoku (26)	1994	62	45	11.3	14.3	0
Tummon (27)	1997	127	53	11.0	14.3	7.1
Guzick (56)	1999	618	231	8.7	21.3[a]	9.3
Sengoku (28)	1999	48	48	14.6	28.6	0
Matorras (29)	2000	290	91	16.9	12.2	8.2
Matorras (30)	2002	209	49	14.4	20.0	0
Williams (31)	2004	62	NA	7.0	0	0
Reindollar (32)	2010	439	169	11.4	10.0	4.0

Note: IUP = intrauterine pregnancy; NA = not available.
[a] Figure represents the combined twin outcomes of SO/IUI and SO/intra-cervical Insemination.

McClamrock. Ovarian stimulation and the multiple epidemic. Fertil Steril 2012.

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A Case for Low Dose Gonadotropin/IUI

Outcome characteristics of representative prospective, randomized trials of SO/IUI using low-dose (≤75 IU) GTs (FSH/hMG).

First author (reference)	Year	Cycles (n)	Participants (n)	Pregnancy/cycle (%)	Twin IUP (%)	High-order IUP (%)
Balasch (59)	1994	94	50	12.8	0	0
Sengoku (28)	1999	49	49	14.3	14.3	0
Goverde (60)	2000	355	85	8.7	29.3	0
Gerli (61)	2004	67 (75 IU)	32	11.9	0	0
		71 (50 IU)	35	12.7	0	0
Dankert (62)	2007	207	67	11.1	4.3	0
Lorusso (63)	2008	184	125	16.3	0	0
Berker (64)[a]	2011	96	96	15.6	13.3	0

Note: Abbreviation as in Table 1.

[a] Used 100 IU for body mass index ≥25 kg/m^2.

McClamrock. Ovarian stimulation and the multiple epidemic. Fertil Steril 2012.

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A Case for Clomiphene/IUI

Outcome characteristics of representative prospective, randomized trials of SO/IUI using clomiphene.

First author (reference)	Year	Cycles (n)	Participants (n)	Pregnancy/cycle (%)	Twin IUP (%)	High-order IUP (%)
Fisch (67)	1989	154	39	2.0	NA	0
Deaton (68)	1990	148	46	9.5	0	0
Karlstrom (69)	1993	17	NA	5.9	0	0
Balasch (59)	1994	98	50	4.0	0	0
Matorras (30)	2002	261	51	6.1	12.5	0
Al-Fozan (70)	2004	123	80	8.9	9.1	0
Dankert (62)	2007	199	71	13.6	3.7	3.7
Badawy (71)	2009	404	207	19.3	2.6	0
Reindollar (32)	2010	1294	475	9.5	5.7	0.81
Abu Hashim (72)	2011	213	67	14.5	6.5	0
Berker (64)	2011	93	93	9.6	0	0
Fouda (73)	2011	210	107	11.4	12.5	0

Note: Abbreviations as in Table 1.

McClamrock. Ovarian stimulation and the multiple epidemic. Fertil Steril 2012.

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FASTT TRIAL

- 503 treatment naïve couples
  - 3 cycles of clomiphene/IUI
    - 3 cycles of FSH/IUI
      - 6 cycles of IVF
  - 6 cycles of IVF
- Per-cycle pregnancy
  - Clomiphene: 9.5%
    - Multiple gestation: 8%
  - Gonadotropin (high dose): 9.8%
    - Multiple gestation: 20%

- **Gonadotropin/IUI does not appear to offer an advantage prior to an IVF cycle**
  - **For women <40, 40% shorter time to pregnancy and a savings of $10,000 per delivery**

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Cost Effectiveness: Old vs. Contemporary Model

- Cost and efficacy per cycle must be considered
- Old model follows a continuum of treatment types and thus incurs additional costs per treatment type

Treatment (<35 years old, unexplained infertility)	Pregnancy Rate	Total Cost (Medical + Drug)	Marginal Cost (Total Cost/Pregnancy Rate)
Clomiphene/IUI	40% over 4 cycles	$4000	$10000
Gonadotropin/IUI	40% over 4 cycles	$12000	$30000
Combined		$16000	$40000
IVF	45% over 1 cycle	$10000	**$22222**

Average UHC costs

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In Vitro Fertilization

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In Vitro Fertilization (IVF)

Preparation
- Ovarian Suppression
  - Prevent spontaneous ovulation
  - Promote synchrony of the growth of ovarian follicles to achieve a cohort of mature eggs
- Ovarian stimulation
  - Gonadotropins
  - Ultrasound monitoring of follicular growth to define timing of egg retrieval

Egg Retrieval
- Ultrasound-guided transvaginal egg retrieval
- The retrieval of 15 oocytes is probably sufficient

Fertilization
- Standard – sperm and egg introduced in a petri dish
- Intracytoplasmic Sperm Injection (ICSI)- sperm injected into the egg
  - Male factor
  - Previous failed fertilization
  - Abnormalities of the zona pellucida (egg "shell")

Embryo Culture & Transfer
- 3 day culture
  - Cleavage stage
- 5 day culture
  - Blastocyst stage

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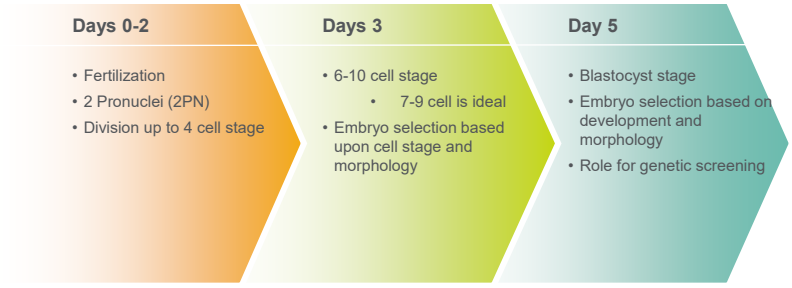
Time Course of Embryo Development



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Stage of Embryo Development

- Most transfers in the US occur at the Blastocyst stage

CLEAVAGE STAGE (generally day 3) – 8 cell

Perfect 8 cell cleavage stage embryo

BLASTOCYST STAGE (generally day 5)

Good looking blastocyst

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Blastocyst Culture and Transfer

- While the transfer of 3 cleavage stage embryos improves pregnancy rates, the multiple gestation rate is also increased
  - There is little to no advantage to transferring more than 3 cleavage stage embryos. Fewer embryos should be transferred to good prognosis patients
- Extended culture to the blastocyst stage improves the selection of embryos with higher implantation potential
  - Blastocyst implantation rates are significantly improved over cleavage stage implantation rates over all age groups
- The transfer of more than 2 blastocysts does not improve pregnancy outcome but increases the risk of a multiple gestation significantly.
- The incidence of monozygotic twinning is increased from 1.4% to 3.1%.
- While the risk of no embryo transfer exists, such a situation may be viewed as an early negative pregnancy test.
  - The vast majority of embryos that fail to achieve expanded blastocyst stage are most likely aneuploid

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The Problem of Multiple Gestations

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Mother/Baby Issues with Multiple Gestations

- Pregnancy loss – early or late
- Preeclampsia
- Gestational diabetes
- Hydramnios
- Anemia
- Antepartum bleeding
- Prolonged hospitalization
- Cesarean delivery
- Postpartum bleeding
- Postpartum cardiomyopathy
- Psychological stress
- Financial stress
- Fetal demise or neonatal death
- Congenital abnormalities
- Preterm Delivery
  - --cerebral palsy
  - --retinopathy
  - --sepsis
  - --intraventricular bleeds
  - --chronic lung disease
  - --necrotizing enterocolitis
  - --hyperbilirubinemia
  - --patent ductus
  - --hypoglycemia
  - --hypocalcemia
  - --prolonged hospitalization
- Long-term disability

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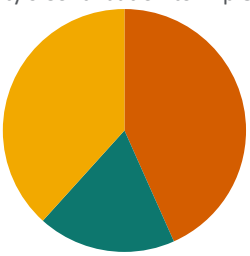
Infertility Trend

Infertility Treatments and NICU Costs

1 in 10 couples of childbearing age seek medical help for infertility[1]

First Year Costs of Care[2]

Infertility's Contribution to Triplet+ Births[3]



Of those seeking treatment, over 50% pursue IVF and super-ovulation, both of which have significant risks of multiples

1. 2008 Merck Serono
2. Reden & Anders analysis of UHC births
3. MMWR Weekly, June 23, 2000

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Decreasing Multiple Gestations

- Avoid gonadotropin/IUI cycles
- Educate consumers regarding the risks of a multiple gestation, including twins
  - Misperception that a twin gestation is without risk
- Elective Single Embryo Transfer (eSET)

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Elective Single Embryo Transfer

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eSET- Why not Always?

- Perception that the pregnancy rate following the transfer of only a single embryo is lower
- Selection
  - Which embryo should be transferred?
  - Decision based upon morphologic evaluation
  - Role for genetic screening to identify a euploid embryo
- Freezing remaining embryos
  - Cost
    - Embryo cryopreservation and storage have variable coverage
    - Benefit redesign mostly accomplished
  - Survival
    - Survival rates following vitrification (rapid freeze technology) now > 90%
  - There is increasing data to support the notion that the transfer of a frozen embryo may be beneficial as the uterine environment may be better compared to a fresh cycle where the uterus has been exposed to high levels of estrogen

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eSET- Why not Always?

- Selection
  - Which embryo should be transferred?

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Single vs. Double Blastocyst Embryo Transfer

- Pregnancy rates for SET are comparable to multiple embryo transfer
- Pregnancy rates are similar for eSET versus double-blastocyst transfer (65%-76% vs. 63%-79%)
  - Multiple gestation rate is significantly higher for double blastocyst transfer (50% - 60%) vs. SET (3%)
  - European data demonstrates a reduction of the multiple gestation rate to ≤1% in some studies
- US data (2019) now demonstrates twin rates of 4.7%-7.1%; triplet rates of 0.1%-0.2%

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Preimplantation Genetic Testing for Aneuploidy (PGT-A)

- The transfer of a single euploid blastocyst results in high implantation and pregnancy rates
- Implantation rate of a euploid embryo remains fairly constant across all age groups
  - The chance for conception therefore is high if a euploid embryo is identified even in older age groups
    - The chance of having a euploid embryo, however, decreases with advancing age
    - Retrospective studies suggest a benefit of PGT-A testing, particularly in women up to age 43 years (improved live-birth rate per cycle start seen in women aged 38-40 years with PGT-A and implantation rates in women 40-43 years of age (implantation rate was 50.9% in euploid embryos compared with unscreened fresh [23.8%] and FET [25.4%] cycles)
    - Female fecundity decreases with increasing age. With aging, chromosome segregation errors during meiotic division are increasingly common and lead to the production of oocytes with an incorrect number of chromosomes, referred to as aneuploidy. Trophectoderm biopsies of >15,000 blastocysts have shown that the rate of aneuploidy steadily increases after age 31 and reaches 85% at age 43

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Aneuploidy and Age

- In an IVF cycle, the possibility of obtaining a high-quality euploid blastocyst and a live birth directly correlates with the number of mature oocytes obtained
- A multicenter longitudinal observational study, the rate of cycles with euploid blastocysts at the age of 44 and 45 was found to be 18% and 5%, respectively. No euploid embryo was found in patients aged >45 years
- In younger women in their early 30s, for example, obtaining even a very small number of mature oocytes (1 to 3) per cycle can still yield a reasonable cumulative live birth rate (21%). In contrast, according to a predictive model using 4,570 women with infertility aged >=38 years, 4 mature oocytes could result in a cumulative live birth rate per fresh IVF cycle of only 16% in women aged 38–39, 12% in women aged 40–41, 5% in women aged 42–43, and 1% in women aged >=44 years
  - Impact of ovarian reserve

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Limitations to PGT-A

- Invasive
  - Requires embryo biopsy
- Expensive
  - Variable coverage by insurance
    - Rationale for coverage – transfer of a single euploid blastocyst can yield an excellent pregnancy rate while minimizing the downstream costs of a multiple gestation
- Few Alternatives
  - Proteomics and Metabolomics
    - While non-invasive, no markers have yet been identified that predict the likelihood of conception
  - Time lapse photography of embryo development
    - May define the proper course of blastocyst formation
    - Does not ensure euploidy

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Fecundity and Age

- Female fecundity decreases with increasing age.
- In an early study to determine the age-based chance of achieving a live birth in women aged >=40 years (n= 2,705, ranging from 40–49 years, with mostly day 3 embryo transfers), the live birth rate per cycle start was 14% at the age of 40. This declined to 1%–2% at the age of 44–45, and to 0 over the age of 45
  - More recent studies demonstrated similar low pregnancy rates (0–2% live births per cycle start) in women aged 44– 45, and no live birth after the age of 45
  - Impact of having a euploid embryo (SART 2019 data):

Age	<35	35-37	38-40	41-42	>42
Live Birth/Intended egg retrieval	46.0%	39.2%	30.1%	18.6%	7.8%
Live Birth/2nd or later transfer	51.8%	50.4%	49.0%	49.1%	47.4%

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Benefit Language

- State Mandates
  - Unlimited IUI cycles
  - Promote “less expensive” treatments prior to IVF
  - Limited IVF cycles in some States
- Health Insurance Plans
  - Promote “less expensive” treatments prior to IVF
  - Variable coverage for cryopreservation
  - Variable coverage for storage

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CONCLUSIONS

Old Treatment Paradigm	• Variety of treatment options • Prolonged treatment times • Relatively low pregnancy rates • High risk for multiple gestations
Contemporary Treatment Paradigm	• Focused on maximizing pregnancy rates in the shortest period of time • In Vitro Fertilization is the treatment of choice for almost all infertility diagnoses • Risk of multiple gestation remains
The Future	• Elective Single Embryo Transfer • Selection of the proper embryo to transfer
How do we get there?	• Education • Redefining Benefit Language • Legislative change- State Mandates • Medical Necessity • Value based contracting

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Any Questions?

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