


Turning Up the Volume on Infertility




IDENTIFYING AND FACILITATING EFFICIENT AND EFFECTIVE CARE

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TODAY'S OBJECTIVES

- Discuss the incidence of infertility and common risk factors for such conditions
- Summarize which patients should be considered for early testing and what testing can be completed in a primary care setting including when to refer to a specialist
- Describe what infertility treatments are available while acknowledging common myths about side effects




Myth-busting style!

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DISCLOSURES

- ❖ Patent (#62/969,880) for methods and compositions for treating and diagnosing PCOS
- ❖ Off-label disclosures: Letrozole for ovulation induction (discussion only)
- ❖ No other relevant financial or professional disclosures



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WHAT IS REI?
... ISN'T IT AN OUTDOOR SUPPLY STORE?!

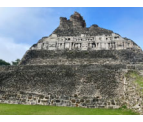


REPRODUCTIVE ENDOCRINOLOGY AND INFERTILITY

- Fellowship trained physicians
 - Bachelors Degree + Med school + OBGYN residency + REI fellowship
- Emphasis on infertility for many practices
- Repro Endo side includes complex problems and care teams
 - Menstrual disorders
 - Mullerian anomalies
 - Polycystic ovary syndrome
 - Congenital adrenal hyperplasia
 - Turner syndrome care
 - Fertility preservation

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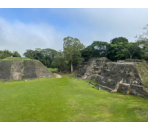


REPRODUCTIVE ENDOCRINOLOGY AND INFERTILITY

- Infertility treatment, clinical discussions and procedurally heavy
 - Egg retrievals
 - Hysterosalpingogram, sonohysterography
 - Embryo transfers
 - Intrauterine inseminations
- PCOS management
- Reproductive surgery
 - Tubal surgery (ie: reversals)
 - Hysteroscopy
 - Laparoscopy
 - Mullerian anomalies

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WHAT IS REI?
... ISN'T IT AN OUTDOOR SUPPLY STORE?!



▪ **What REI as a field is NOT:**

- ...an IVF factory
- ...always cost prohibitive
- ..."two for the price of one" shop
- ...a substitute for general GYN or PCP care

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REPRODUCTIVE ENDOCRINOLOGY AND INFERTILITY — CLINICAL PRACTICE

Special populations...to name a few

- LGBTQ+
- Single parent by choice
- Cancer warriors and survivors
- Fertility preservation patient
- Victims of abuse
- Pediatric and adolescent patients
- **Every person**
- **Every couple**



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INTRODUCTION - DEFINITIONS AND FAST FACTS

Infertility: inability to conceive after 1 year of unprotected intercourse of reasonable frequency

- Primary: no prior pregnancies
- Secondary: at least one prior conception

10-15% of all couples suffer from infertility = 1:8

In women attempting conception:

- 50% will be pregnant at 3 mo
- 75% at 6 mo
- >85% at 1 year

Fertility decreases with maternal age

Rule of thirds:

- 1/3 cases attributed to female, 1/3 male, 1/3 both partners

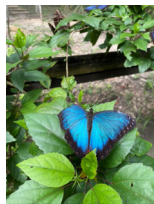


Taylor et al 2020

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INFERTILITY IN REAL LIFE IS...

- Isolating
- Self-doubt instigating
- A rollercoaster of emotions
- Anxiety provoking, depression deepening
- Filled with unfair judgments and comparisons
- And among many other things, surrounded by myths and misconceptions



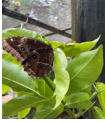
The Lasting Trauma of Infertility

Even when it ends with a healthy baby, a long struggle to conceive may exact a brutal toll.

The New York Times

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MISCONCEPTION #1: EVERYONE IS GETTING PREGNANT!



“Why rush it?!”

| Months of exposure | % Pregnant |
|--------------------|------------|
| 3 months | 57% |
| 6 months | 72% |
| 1 year | 85% |
| 2 years | 93% |

Table adapted from Speroff 2005

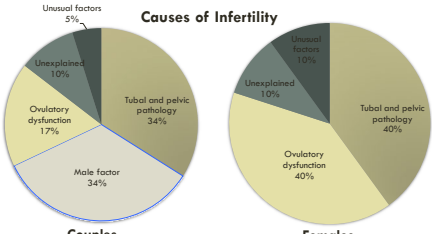
When to seek evaluation:

...in general:

- Any couple with ≥ 12 months regular, unprotected intercourse without conception*
- Female age 35 with ≥ 6 months without conception*

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MISCONCEPTION #1: EVERYONE IS GETTING PREGNANT!



Causes of Infertility


Couples: Unusual factors 5%, Unexplained 10%, Ovarian dysfunction 17%, Male factor 34%, Tubal and pelvic pathology 34%

Females: Unusual factors 10%, Unexplained 10%, Ovarian dysfunction 40%, Tubal and pelvic pathology 40%

Graphs adapted from Taylor 2022

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MISCONCEPTION #1: EVERYONE IS GETTING PREGNANT!



Initial Evaluation Highlights – History

- G/P's
- infertility history?
- pregnancy complications
- Detailed menstrual and sexual histories history
 - Coital frequency, sexual dysfunction or dyspareunia
 - Pelvic infections, cervical dysplasia tx?
 - Galactorrhea
- Medical or surgical history?
- Medications?

• Occupation/environmental exposures

• Family history?

• Birth defects, developmental delay, early menopause

Initial Evaluation Highlights – Physical

- Height, weight, BMI
- Blood pressure/heart rate
- Thyroid, signs of androgen excess, bimanual findings

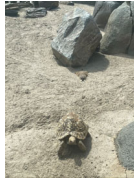
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"INFERTILITY ALARM SYMPTOMS" ... REFER EARLY*:

FEMALE PARTNER:

- Irregular cycles
- Hx of pelvic inflammatory disease
- Hx of endometriosis
- IBD (Crohn's or Ulcerative colitis)
- Hx gonadotoxic therapies or gonadectomy
- Hx infertility with prior partner
- Hx multiple biochemical pregnancies
- Interested in fertility preservation
- Age >38*

***What does "early" mean?**
Sooner than usual age recommendation:
<35 = 12 months TTC
≥ 35 = 6 months TTC



MALE PARTNER:

- Current or history of testosterone use (assess SA)
- Hx significant genital trauma or surgery
- Hx infertility with prior partner

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**MISCONCEPTION #2:
 OUR SEX LIFE? NO WAY!**



Little known fact: Humans are not highly fertile primates!

*For comparison – baboon cycle fecundity ranges ~80%

Fecundability: probability that a cycle will result in pregnancy

Fecundity: probability that cycle will result in **live birth**

***Normal human couples: ~20% (... = 20% chance/month!)**

***does not exceed ~35% even when coitus is carefully timed**

***Important benchmark for counseling re: treatment options and efficacy of each**

Speroff 2005

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**MISCONCEPTION #2:
 OUR SEX LIFE? NO WAY!**

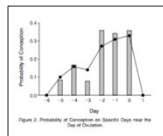


Figure 2. Probability of Conception on Specific Days near the Day of Ovulation.

Coital frequency is important!

- Every 1-2 days during fertile window or general recommendation for twice weekly likely suffice without adding undue stress
- Timed intercourse may be recommended in certain treatment scenarios

Coitus must approximate/antecede ovulation

- ~All pregnancies result from intercourse occurring sometime within the 6-day interval ending on day of ovulation

"Fertile window"

- Normal sperm can fertilize an egg for ~3-5 days
- Successful oocyte fertilization only ~12-24hrs after ovulation

Speroff 2005

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**MISCONCEPTION #3:
IT'S ANYONE'S "FAULT"!**

Male factor contributory to infertility in up to 35% of couples!

What testing can I do?!

Semen analysis is always an appropriate and important initial step in evaluation

- Should include reproductive hx and two semen analyses (if first is abnormal)
- Goals are to identify:
 - Correctable conditions, irreversible conditions, life or health-threatening conditions, genetic abnormalities
- Important historical points:
 - Medical hx: childhood illnesses, testicular trauma/torsion, medications, supplements, hx radiation or chemo
 - Sexual history: coitus, lubricants, erectile dysfunction
 - Environmental exposures: tobacco, marijuana, steroids, chronic heat exposure

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**MISCONCEPTION #3:
IT'S ANYONE'S "FAULT"!**

Ovulatory dysfunction is responsible for 40% of female infertility

What testing can I do?!

Is she actually ovulating? Taking the history is your best tool!

...regular, monthly bleeding with normal flow = typically, ovulation occurring 14 days prior to period

...but if unclear, how do we confirm? Labs! CD21 progesterone level ...if negative, can repeat in 1 week!

...patients can also try home ovulation predictor kits

- check mid-day urine daily, starting ~CD7 and stop when positive

Can you have a "period" without ovulating? – yes!

- Why do anovulatory patients bleed?
 - Atrophic (thin) lining
 - Sloughing at regular intervals due to unopposed estrogen/thickened lining → get an ultrasound

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**MISCONCEPTION #3:
IT'S ANYONE'S "FAULT"!**

Ovulatory dysfunction is responsible for 40% of female infertility

I suspect polycystic ovary syndrome (PCOS)...

But ovulation predictor kits results are variable...

- Ovulation predictor kits measure LH
- LH levels in PCOS? - often elevated!
- What levels do commercial OPK kits start turning positive? ~15! ...think false positive!


But she doesn't have obesity, hirsutism, or acne...it can't be PCOS!

- Lean PCOS
- ...and she's been on OCPs x10 years! – ...recall this is a therapy for androgen PCO symptoms

PCOS can be incredibly confusing! Do not hesitate to refer these ladies to us early in their care so precious time does not slip by while "waiting" on their periods to show-up and/or regulate!

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MISCONCEPTION #3: IT'S ANYONE'S FAULT!



What other female infertility tests are out there?!

- **Ovarian reserve testing = egg count assessments**
 - Cycle day 3 labs: estradiol, FSH
 - Antimullerian hormone level (AMH) = any cycle day!
- **Hysterosalpingogram (HSG) = fallopian tube test**
 - Risk factors for abnormal tubes?
 - History of STIs, PID, endometriosis, appendicitis, IBD (UC and Crohn's), hx of multiple pelvic surgeries, prior ectopic pregnancies*
 - *Recurrent pregnancy loss patients with all early biochemical losses
 - If clinical scenario is clearly ovulatory dysfunction, okay to defer for ~4-6 treatment cycles if no risk factors

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MISCONCEPTION #4: NORMAL REPRODUCTIVE TRACT = NO ISSUES

In addition to factors that are yet unexplained, obesity and environmental factors can also impact fertility:

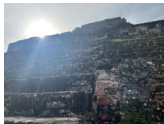
| Factor | Impact on Fertility |
|-----------------------|--|
| Obesity (BMI >35) | 2-fold increase time to conception (TTC) |
| Underweight (BMI <19) | 4-fold increase TTC |
| Tobacco use | 60% increase RR of infertility |
| Alcohol use (>2/day) | 60% increase RR of infertility |
| Illicit drugs | 70% increase RR of infertility |
| Toxins | 40% increase RR of infertility |
| Caffeine (>250mg/day) | 45% decrease fecundability |

Preconception counseling! – optimize where you can!

Adapted from Williams Gynecology, Hoffman 2012

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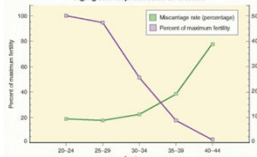
MISCONCEPTION #5: 40 IS THE NEW 30!!



Age isn't just a number in fertility - sadly!

- Studies suggest fertility peaks between ages 20-24, decreases slowly age 30-32, and then declines progressively
- Additionally, miscarriage rates rise progressively with age

Aging and Reproduction in Women



The same patterns are observed in ART pregnancies!

Live birth rate per untested embryo:

- age <35: 45.6%
- age 35-37: 27.1%
- age 38-40: 16.0%
- age 43-44: 8.4%

Percent of maximum fertility

Miscarriage rate (percentage)


Age in years

Difficulties and infertility

Taylor 2022

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**MISCONCEPTION #5:
40 IS THE NEW 30!!**



...but XYZ celebrity just had twins at 45!!

- Although many celebrities have publicly praised the option of gestational carrier for the development of their families, few have discussed oocyte donation as a component

Alternate options for diminished ovarian reserve:


- Oocyte donation
- Embryo adoption
- Traditional adoption
- Foster

- For ~95% of women by age 30, only 12% of maximum pre-birth non-growing follicles remain
- Women age 40: only 3% remain

Taylor 2022

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**MISCONCEPTION #6:
IVF?! I DON'T WANT TWINS + !!**



Assisted Reproductive Technologies (ART): any fertility treatments where both eggs and sperm are handled

In vitro fertilization (IVF)


- Most common ART procedure, first used in the US in 1980
- Many indications: tubal factor, severe male factor, unexplained, fertility preservation, preimplantation genetic diagnosis
 - IVF remains the most effective treatment for unexplained

Incidence of multifetal gestation in the US initially increased dramatically, ~76% between 1980 and 2009, now w/stabilization/downtrend

- Initial increase attributed to two things:
 - Shift toward older maternal age at conception
 - Increased use of ART
- Downtrend in large part due to single embryo transfer

Taylor 2022

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**MISCONCEPTION #6:
IVF?! I DON'T WANT TWINS + !!**

Misconceptions?!

- Higher order multiples
- IVF as primary culprit

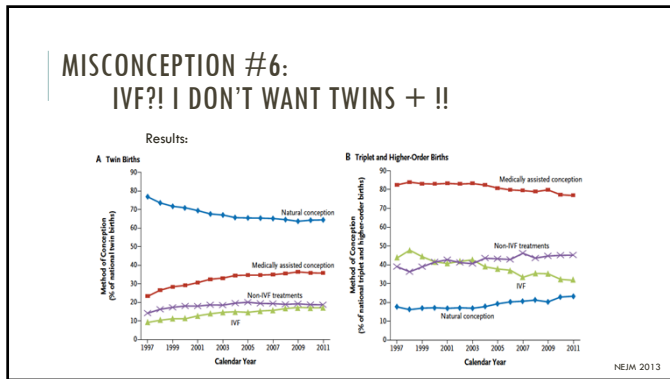
NEJM 2013 – Kulkarni, Adasha, et al (CDC)

- Retrospective analysis of publically available birth data from 1971-2011 to assess multiple birth rates
 - Results adjusted for maternal age
 - Evaluated IVF rates as well as medically assisted conception (non-IVF fertility treatments)

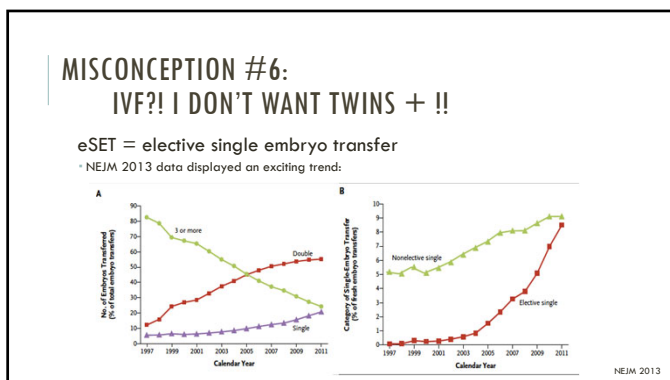
1998 - The Society for Assisted Reproductive Technology (SART) first developed practice guidelines, aiming to reduce multiple births

- In light of this, Kulkarni, Adasha, et al performed a test for trend from 1998-2011 as they would expect a change in proportion of multiples thereafter

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MISCONCEPTION #6: IVF?! I DON'T WANT TWINS + !!

SART data from 2019:
 * From 2010-2019, % of embryo transfers resulting in singleton increased from 22.6 → 34.4% and twin decreased from 9.0 to 2.7%

Important considerations/factors

- * eSET
 - Population age – often performed in younger patients
 - Insurance coverage
 - Preimplantation genetic testing


Recommendations for the limit to the number of embryos to transfer

| Regimen | Age | | | |
|--------------------------------|------|-------|-------|-------|
| | < 35 | 35-37 | 38-42 | 43-42 |
| Controlled ovarian stimulation | 1 | 1 | 1 | 1 |
| IVF | 1 | 1 | 1 | 1 |
| IVF or IVF with PGT-A | ≤ 2 | ≤ 3 | ≤ 4 | ≤ 5 |
| IVF | 1 | 1 | 1 | 1 |
| IVF with PGT-A | 1 | 1 | 1 | 1 |
| IVF or IVF with PGT-A | ≤ 2 | ≤ 3 | ≤ 3 | ≤ 3 |

ESHRE 2015, Forman 2013, ASRM Practice Committee 2021

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MISCONCEPTION #6:
IVF?! I DON'T WANT TWINS + !!




Important other treatment considerations/factors

- Ovulation induction and stimulation
 - Risk of twins
 - Oral agents: ~10%
 - Injections: ~20%
 - Difficult to prevent multiple births – unpredictable follicular growth dynamics
- Adherence to prudent practice patterns
 - Low-dose gonadotropins
 - Close monitoring of follicular number on oral stimulation cycles
 - Cancellation does not equal failure

Williams 2014

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MISCONCEPTION #7:
TWO FOR THE PRICE OF ONE!



Not a "BOGO" offer!

Multifetal gestations associated with increased fetal and infant morbidity and mortality → related to complications of prematurity:


- ~5 fold increased risk of stillbirth
- ~7 fold increased risk of neonatal death
- 6x more likely to have preterm delivery
 - 3x more likely to deliver <32wks GA

Although parents may appear to be saving on infertility treatment costs, care for preterm infants is up to 10x greater than for term infants!

Williams 2014

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MISCONCEPTION #7:
TWO FOR THE PRICE OF ONE!




Maternal morbidity and mortality

- Medical complications more common in multifetal gestations:
 - Hyperemesis gravidarum
 - Gestational diabetes mellitus
 - Hypertensive disorders
 - Proportional to total fetal number
 - Anemia
 - Hemorrhage
 - Cesarean delivery
 - Postpartum depression

Williams 2014

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MISCONCEPTION #8: BREAKING THE BANK



While IVF itself can be quite expensive, infertility treatment doesn't mean you have to spend your lifefavings to even seek therapy!

Interesting trends:

- High cost of living does not equate to high treatment costs
- Insurance coverage is variable
- Increasing numbers of employers covering care
 - Part time vs full time

Questions to ask:


- Insurance! *Wikoi*, if anything, does your coverage include
- Are medications, tests, lab work, consultations included?
 - Limited treatment? If so, what? Lifetime max? Smart cycles?
- Does the clinic offer financial counseling and/or payment plans?

Resource: RESOLVE.ORG → MAKING TREATMENT AFFORDABLE

Lebovic 2014

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MISCONCEPTION #9: HUMAN PHARMACY



Yes, injectable medications can make a person feel a bit like a pharmacy - but there are less invasive options as starting points and this is **MOST OFTEN** the initial treatment!

Oral medications

- Clomiphene citrate
- Letrozole

Ovarian stimulation regimen goals:

- Low cancellation rate
- Minimize drug costs
- Minimize risks and side effects
- Require limited monitoring for practical convenience
- Maximize singleton pregnancy rates

Initial treatment may often (but not always) include intrauterine insemination (IUI)

IUI helps increase the chances that good sperm and good egg(s) may meet one another through use of the patient's own fallopian tube and therefore improve pregnancy rate

...this is NOT an IVF procedure!

Taylor 2022

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MISCONCEPTION #10: JUST RELAX



Controversial!

Although severe stress can result in anovulation and resultant infertility, less significant stress is poorly understood as it relates to infertility

- At present, there is little evidence supporting the "just relax and you won't even need infertility treatment" perspective

Treatment options for stress management

- Psychological interventions
 - Mindfulness based cognitive therapy
 - Mind/Body approach
- Pharmacologic
 - Adjunctive
 - Acupuncture
 - Relaxation techniques
- Counseling!
 - Couples therapy and support groups

Williams 2005

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REFERRAL PEARLS



...three main questions are relevant when trying to decide on subspecialist referral:

- Who?
- When?
- To Whom?

Unfortunately, the answer isn't always simple but there are a few must-consider clinical scenarios to be aware of

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REFERRAL PEARLS

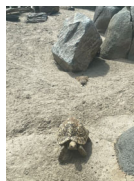


Who?

- Major medical comorbidities
 - Diabetes, hypertension, etc
- Abnormal bleeding/periods, especially if transfusion history
- Infertility history or prolonged attempt at conception
 - *PCOS
 - Especially if ≥ 35 years
- Recurrent pregnancy loss
 - Defined: 2 or more clinical losses

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REFERRAL PEARLS



WHEN

- Any couple with ≥ 12 months regular, unprotected intercourse without conception*
- Female age 35 with ≥ 6 months without conception*
- *Refer earlier for:

FEMALE PARTNER:

- Irregular cycles
- Hx of pelvic inflammatory disease
- Hx of endometriosis
- IBD (Crohn's or Ulcerative colitis)
- Hx gonadotoxic therapies or gonadectomy
- Hx infertility with prior partner

MALE PARTNER:

- Hx multiple biochemical pregnancies
- Interested in fertility preservation
- Age $>38^*$
- Current or history of testosterone use (assess SA)
- Hx significant genital trauma or surgery
- Hx infertility with prior partner

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REFRRAL PEARLS

To whom?

- OBGYN specialist
- REI
 - Infertility
 - RPL
 - Severe endometriosis
 - Complex endocrinologic history
- Hematologist
 - Diagnosed or suspected bleeding disorder



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QUESTIONS?



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THANK YOU!

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