Understanding Heat Stress Through Bovine Assisted Reproductive Techniques

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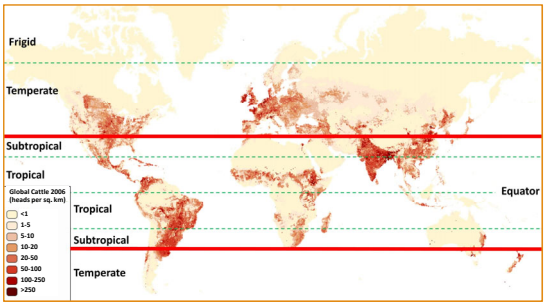
Heat Stress is a Widespread Problem



First published from [1]Robinson et al. 2014 with additional info from Mavridou et al. 2018 via application.geo-wiki.org

Heat Stress is an Expensive Problem

First published from [1]Robinson et al. 2014 with additional info from Mavridou et al. 2018 via application.geo-wiki.org

Heat Stress Decreases Fertility



Hyperthermia

Images: iStock, Old Farmer's Almanac, overstock.com, dsm.com

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The Problem Is Complicated

Heat Stress Component
- Stress
- Temperature
  - Degree
  - Duration
  - Timing

Fertility Component
- Male Factor
- Female Factor
- Benchmark
  - Pregnancy Outcomes
  - Pregnancy Loss
  - Gestational Epigenetics

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Heat Stress Component
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- Temperature
  - Degree
  - Duration
  - Timing

2.5% ↓ per 10 unit THI ↑[3]

Fertility Component
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The Problem Is Complicated

Heat Stress Component
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Summer vs Acute? [4-6]

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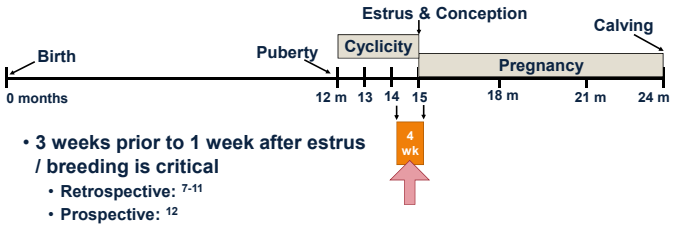
Timing of Increased Body Temperature Matters



- 3 weeks prior to 1 week after estrus / breeding is critical
  - Retrospective: [7-11]
  - Prospective: [12]

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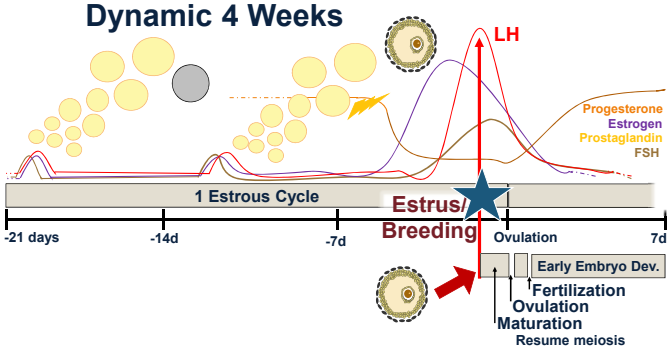
Dynamic 4 Weeks



ARTs Critical to Investigate

- Independent variable: "heat" of heat stress
  - Vs. general stress, decreased food intake, decreased production….
- Dependent variable: the thing its acting on
  - Embryo vs. uterus / oviduct
  - Oocyte vs. granulosa cells

Images: anypromo.com

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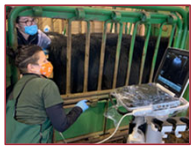
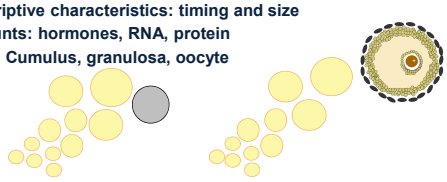
ARTs Critical to Investigate

- Experimental design
  - Semen cryopreservation / AI
  - Estrus synchronization
  - Embryo flush
  - Embryo transfer
  - *In vitro* embryo production (IVP)
  - OPU
  - SCNT
- Sampling
  - Embryo flush
  - IVP
  - OPU



Isolation through Estrus Synch

- Heat stress chambers with or without additional ARTs
- At least 10 studies from 1980's to 2022[5,13-21]
- Follicle dynamics, luteal dynamics, endocrine changes
  - Descriptive characteristics: timing and size
  - Amounts: hormones, RNA, protein
  - Cells: Cumulus, granulosa, oocyte



Isolation through Estrus Synch

- Require careful extrapolation
  - Multiple possible effects
    - Post-insemination heat stress: embryo, oviduct, uterus, CL?
  - Delineating physiologic events
    - Peak of estradiol may occur 4 hr prior to 8 hr after LH surge
    - Peak of LH may occur at or up 8 hr after standing estrus
    - LH surge critical inducer of oocyte maturation
  - Limited number of animals
    - [13-14]: n= 29 or 16 with max 2 in chambers at any time

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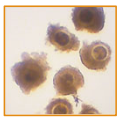
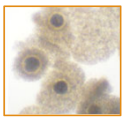
Isolation through IVP

- Isolate events
  - Oocyte maturation
  - Fertilization
  - Early embryo development





- Specific levels of "heat" at defined durations
- Abattoir derived = large numbers
- OPU = collection of follicular fluid and ovarian cells

Images: Maksura et al. 2020

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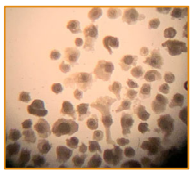
What have we learned?



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Heat Stress on Luteal Tissue

- Seasonal heat stress on circulating P4
  - Increased[6,22]
  - Decreased[23]
  - No effects[4,15-16,18,24]

- Estrus synch:
  - Delayed luteal regression[16]
    - Authors hypothesized due to follicular dynamics
  - Induced luteal regression not effected[19]

Image: Pieterse MC 1999

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Heat Stress on Luteal Tissue

- Luteal cells develop from theca and granulosa
- In HS, theca have reduced androstenedione production[5]

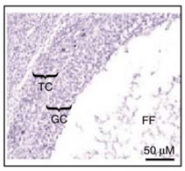

Image: Maillard et al. 2011

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Heat Stress on Luteal Tissue

- Cultured granulosa cells = oxidative stress and apoptosis[25-28]
  - For as short as 2 hrs at + 1.5°C
- Synchronized cows = No evidence of oxidative stress and apoptosis
  - 4 days around estrus[29]
  - + OPU: 12 hours after the LH surge[21]
  - Extracellular matrix remodeling, angiogenesis
    - Important for normal CL formation

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Heat Stress on Luteal Tissue

- Data mixed and generally inconclusive
- Seems unlikely that the driver of reduced fertility is CL dynamics

Image: Pieterse MC 1999

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Heat Stress on Pre-LH Surge Period

- Seasonal heat stress on dominant follicle diameter
  - Decreased[6,11]
  - No effect[4-5]
- 7 day HS in synch + OPU[17]
  - No effect on intrafollicular P4, E2, Heat Shock Protein 90
    - Similar findings to others[4-5,30]
  - Increased total protein concentration
  - = Not consistent with atresia

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Heat Stress on Pre-LH Surge Period

- IVP of oocytes from different seasons
  - IVP: maturation onward at TN temperatures
    - Superstim + OPU[31]
    - Abbatoir[32-34]
  - = Decreased embryonic development
  - Effect genes related to metaphase arrest, folliculogenesis, energy metabolism, cytoskeleton organization, DNA repair[35]
- IVP + meiotic inhibitors: 12 h HS = decreased development[36]

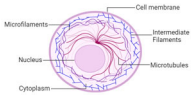

Image: overallscience.com

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Heat Stress on Pre-LH Surge Period

- IVP: Acute on Chronic vs Acute = less impacted = induced thermotolerance[37]
- IVP + treatment with extracellular vesicles[38]
  - EV's derived from HS or TN cow follicular fluid
  - IVP at TN conditions
  - = Impacts on oocyte and CC genes
  - = Not meiotic progression
  - = Not DNA integrity

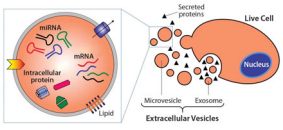
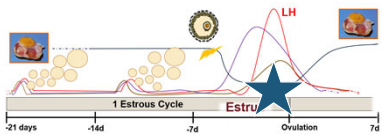


Image: PioProcess International

Heat Stress on Pre-LH Surge Period

- HS prior to LH surge can impact the oocyte to reduce embryonic development
  - Even if post-LH surge at TN conditions
  - Even at as little as 12 hr just prior to LH surge



Heat Stress on Post-LH Surge Period

- Superovulated heifers HS between estrus and insemination
  - Reduced embryo development
  - Increased abnormalities

P < 0.01
[14]Putney et al. 1989

Embryo Quality	Thermoneutral	HS during 1st 10h
Good to Excellent	47%	4%
Poor to Fair	42%	76%
Unfertilized Ova	11%	20%

Heat Stress on Post-LH Surge Period

- Estrus expression not perfectly timed with LH surge
- LH Surge = induces oocyte maturation & ovulation
  - Oocyte maturation ~24 h in IVP
  - LH surge to ovulation ~30 h in cows
- IVP HS for 22 hrs: reduced blastocyst rate by 70%[39]

Heat Stress on Post-LH Surge Period

- IVP HS in first 12 h of maturation
  - No effect on cleavage in majority of studies[40-43,45-46,48]
  - Blastocysts reduced by 35 to 68%[39-40,46-49]
- *Bos indicus* or Xs
  - Blastocyst development reduced by 39 to 50% (14h)[50]

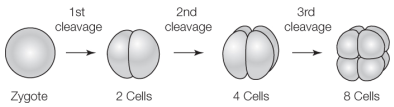


Image: Macmillan Learning

Heat Stress on Post-LH Surge Period

- IVP +/- OPU mainstay of investigation
- EV's impact embryonic development[51]
- Reduced oocyte meiotic progression (22-24 hr)[39,52]
- Accelerated meiotic progression[47]
  - Accompanying accelerated cortical granule distribution
    - Required to prevent polyspermy
  - 7h earlier insemination prevented embryo development reductions
    - Not practical b/c oocyte would still be in follicle but cool!

Heat Stress on Post-LH Surge Period

- Oocyte impacted in other ways:
  - Increased zona pellucida damage (22 h)[39]
  - Increased ATP content (12 h)[46]
  - Reduced protein synthesis (12 h)[40]
  - Reduced glutathione content (12 h)[46]
- *Bos indicus*:
  - Increased apoptosis and decreased mitochondrial activity (14 h)[50]

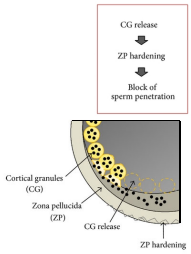


Image: Hindawai BioMed Research International

Cumulus & Oocyte Intimately Associated

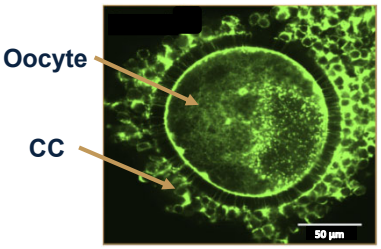
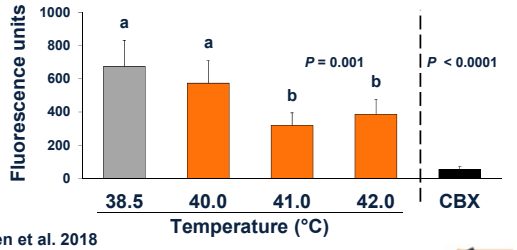


Image: Soto-Heras et al. 2019

Important for:
- LH Signal transmission
- Fertility post-ov

IVP: HS Reduced Communication

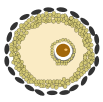


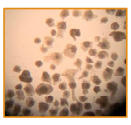
[53]Campen et al. 2018

Calcein Transfer: Cumulus to Oocyte;
CBX: Carbenoxolone; Gap Junction Inhibitor

Heat Stress on Post-LH Surge Period

- TN IVP: COCs produce progesterone after LH Surge
  - CC derived from granulosa cells
  - Associated with meiotic progression
  - Likely too dilute to measure in cow follicular fluid[20]
- HS increased progesterone production (6-12 h)[53-55]





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Heat Stress on Post-LH Surge Period

- CC expansion inhibited (24 h)[52]
  - Not seen in our lab with 12 h
- Many alterations of CC transcripts (12 h)[21,54]
  - Associated with cell junctions, oocyte developmental competence, cell-cycle regulation

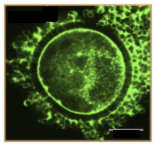
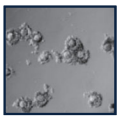
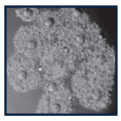


Image: Soto-Heras et al. 2019

Interleukin-6

- Inflammatory cytokine
- Under thermoneutral conditions using IVP:
  - Cumulus cell expansion
  - Progesterone levels
  - Timing of oocyte maturation





Images: Liu et al. 2009

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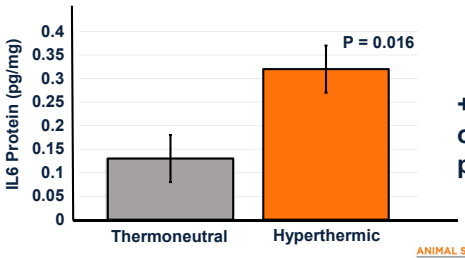
IL6 in the Follicular Fluid (Synch + OPU)



+ 34 other proteins!

[20]Rispoli et al. 2019

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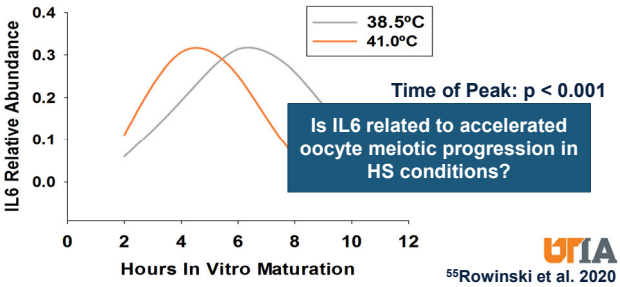
IL6 Transcript in the COC (IVP)



Time of Peak: $p < 0.001$

Is IL6 related to accelerated oocyte meiotic progression in HS conditions?

[55]Rowinski et al. 2020

Heat Stress on Post-LH Surge Period

- Shorter periods of time….?
  - 6 h = reduced cleavage but not blastocysts[56]
  - 6 h = reduced cleavage and blastocyst rates[55]
  - 6 h = no effect[39]
  - 4 or 6 h = no effect[55]
    - Numerically higher blastocyst rates with HS than controls
  - 1 h at end of maturation = no effect[57]
  - 4 h at end of maturation = reduced blastocyst rates but not cleavage[58]

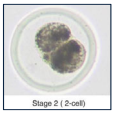


Image: Brad Lindsey

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Heat Stress on Post-LH Surge Period

- Somatic Cell Nuclear Transfer[59]
- Swapped nuclei between Holstein and thermotolerant Taiwan Native Yellow Cows
- 43°C for 1 h impacted cytoplasm to a greater extent than nucleus

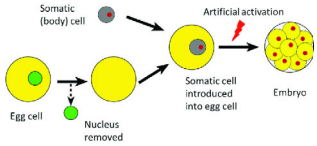

Image: Pepper et al. 2015

Heat Stress on Post-LH Surge Period

- Periods as little as 12 h after the LH Surge have devastating consequences on fertility

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Heat Stress on Ovulation

- HS from days 11-21 of cycle reduced ovulation rates[15]
- HS heifers more likely to have a third wave[16]
  - Ovulation rates between second and third wave were not compared
- Single cycle = no effect[18,60]

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Heat Stress on Ovulation

- Superovulated Holstein-Thai cows has reduced ovulation rate but similar number of total CL[61]
  - = more anovulatory follicles
- Reduced embryo recovery after superovulation in HS heifers (10h post-LH)[14]

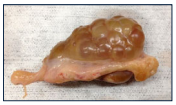

Image: Denicol AC 2013

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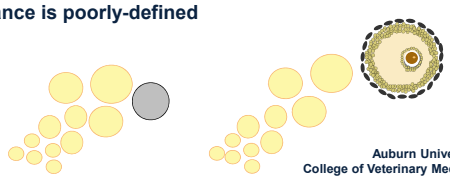
Heat Stress on Ovulation

- Seasonal HS reduced ovulation[62]
- Physiologic mechanisms unknown
- Importance is poorly-defined



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Heat Stress Post-Ovulation

- Post-ovulatory COC, Post-Ejaculated sperm, Fertilization
- Oviduct, Vagina, Cervix, Uterus
- Fertilization often defined as number of embryos
  - Development to 8-cell stage can occur in unfertilized ova[63]
- IVF HS = decreased percent of penetrated oocytes[52]

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Heat Stress Post-Ovulation

- HS cryopreserved sperm[64]
  - Reduced motility
  - No effect on DNA integrity
  - No effect on presence of intact acrosome
- HS sperm prior to TN IVF
  - Sperm penetration was not affected[65]
  - Polyspermy increased[65] or decreased[66]

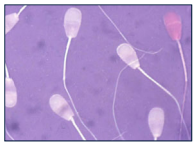

Image: IVIS

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Heat Stress on Early Embryo

- Superovulation, IVP and Embryo Transfer
- HS in first 7 days = higher incidence of abnormalities and developmental delays[13]

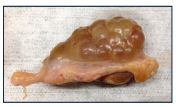

Image: Denicol AC 2013

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Heat Stress on Early Embryo

- 12 h HS reduces development of 2-, 4- and 8- cell embryos[41]
- By d3 of development, embryos fairly resistant
  - Completely resistant by d7[67]
  - Embryo transfer to by-pass HS effects[68-71]

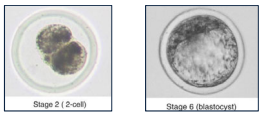

Image: Brad Lindsey

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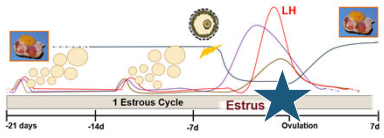
Clinical Implications

1. Synchronization of estrus +/- FTAI to increase the number of females being inseminated
   - Cryopreservation of sperm during cool months
2. Minimizing HS during full cycle prior is important



Clinical Implications

3. Superovulation and IVP demonstrate even acute HS near estrus has devastating consequences
   - Effects on ejaculated sperm appear to be minor compared to oocyte
4. Embryo transfer to increase summer pregnancies
   - Cryopreservation of embryos

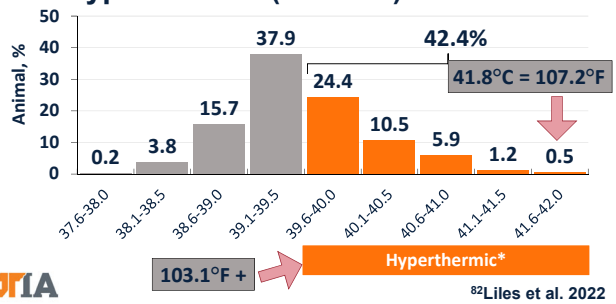
Clinical Implications

5. What is the normal temperature of a cow?

100.0°F = 37.8°C
101.5°F = 38.5°C
102.5°F = 39.1°C

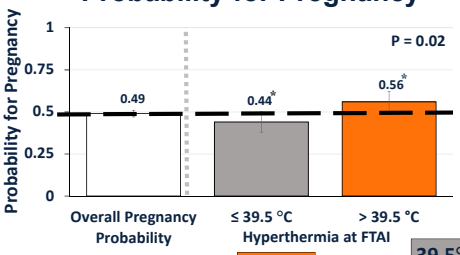
Avg Change in Temperature During Estrus			
First Author	Year	Type	Mean Temp. Change (°C)
Suthar[72]	2011	Dairy	+0.3
Higaki[73]	2019	Beef	+0.4
Randi[74]	2018	Beef	+0.4
Cooper-Prado[75]	2011	Beef	+0.5
Redden[76]	1993	Dairy	+0.7
Miura[77]	2017	Beef	+0.9
Kyle[78]	1998	Beef	+0.9
Lewis[79]	1984	Dairy	+1.0
Fisher[80]	2008	Dairy	+1.2
Piccione[81]	2003	Dairy	+1.3

Hyperthermia (Not HS!) at FTAI



[82]Liles et al. 2022

Hyperthermia at FTAI Increases Probability for Pregnancy



[82]Liles et al. 2022

n = 427

39.5°C = 103.1°F

Clinical Implications

6. The problem is complicated = a lot of unknowns left to be discovered
   - What is similar / different between acute and chronic heat stress?
   - At what point does acute become chronic?
     - Same for every point in the cycle?
   - What temperature is too hot for even acute periods of time?
   - Are effects of heat stress preventable? Reversible?
7. ARTs likely to continue to be fundamental to investigation and solutions

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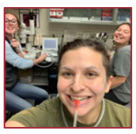
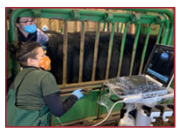

Thank you! Questions?

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