we are honored to have dr ann zycheck

dr zyck is a board certified

pediatrician and a pediatric clinical

pharmacologist who currently serves as

deputy director of the office of

clinical research at the nih

and received a bachelor degree in

pharmacy from duquesne university and a

doctorate of pharmacy degree from state

university of new york at buffalo

she then completed postdoctoral

fellowship training at saint jude

childrens research hospital

after that she served as assistant

professor at the university of colorado

school of pharmacy and a clinical

pharmacist at national jewish hospital

in 99

ann entered medical school

at the university of pittsburgh in 99

completed residency in pediatrics at

childrens hospital in pittsburgh

she practiced primary care pediatrics

for two years and then continued her

training in pediatric clinical

pharmacology at stanford university

she subsequently joined the fdas office

of clinical pharmacology and

biopharmaceutics

in 00 she joined the national

institute of child health and human

development

we know you will enjoy dr zychecks

lecture

hi

my name is dr ann zicek im a

pediatrician clinical pharmacologist and

i will be speaking today about obstetric

pharmacology

for disclosures i have no conflicts of

interest to disclose and my presentation

reflects my views only not those of the

nih or the us federal government

the topics i wanted to talk about today

include medical conditions and medical

or medication use in pregnancy

physiologic changes in pregnancy drug

metabolizing enzymes and transporters

both maternal and fetal

maternal fetal drug transfer

pharmacodynamic changes in pregnancy

medical conditions and medication use in

pregnancy

regarding

fetal and maternal conditions

teratogenicity and preclinical models

and research needs

i wanted to start first by talking about

the medical conditions that occur in

pregnancy this will sort of set the

stage for what i want to talk about

the conditions that are caused by or

coexisting in pregnancy include

pregnancyinduced hypertension

preeclampsia preterm labor gestational

diabetes depression infections pain and

nausea and vomiting of pregnancy this is

not allinclusive but this is

a fair number

preexisting medical conditions include

hypertension

diabetes depression seizure disorder

cancer endocrine disorders substance

abuse and autoimmune disorders

this is a paper talking about the

medication use

during pregnancy and the medication use

just in the first trimester and whats

interesting here as you can see that

these curves from

9 through 00 show a rise

not only in

the numbers of medications that women

are taking during the first trimester

but the number of medications that women

are taking at any time during the

pregnancy and what had

started at

somewhere between one and two

medications during the first trimester

has now increased to somewhere between

two and three medications in the first

trimester and at any time during the

pregnancy from two to three medications

in 9 up to now between four and five

medications during the pregnancy

and the next question is what

medications are women taking during

pregnancy and ive

put red boxes around the drugs that are

not antiinfective so you can see that

the majority of medications that women

are taking are antiinfectives but you

can also see theres a use of

pain medications such as codeine

hydrocodone

ibuprofen acetaminophen

medications for nausea and vomiting i

assume

including promethazine and

metaclopramide as well as medications

for asthma treatment

in terms of medication exposure um

the cdc uh

indicated that about four million births

took place in 0

and antiepileptic drugs are used in

about percent of pregnancies

yielding about 90 000 children who were

exposed to antiepileptic drugs

asthma

00 000

uh fetuses exposed to asthma medications

antidepressants including the specific

serotonin excuse me selective serotonin

reuptake inhibitors six percent or about

0 000 fetuses exposed to

antidepressants so theres a fair amount

of fetal medication exposure

this is a paper from 00 showing the

obstetric drug pipeline

and what this paper showed was that

there were vanishingly few new drugs

being developed for obstetric

indications

the paper was very interesting it

compared

the number of drugs in the pipeline for

obstetric conditions

cardiovascular conditions in other words

high frequency conditions

and a myotrophic lateral sclerosis for a

rare adult indication and what you can

see is that

even though there are four million

births per year there are only new

drugs being

developed for obstetric indications 0

for cardiovascular indications

and for a myotrophic lateral

sclerosis again indicating that there

are not many drugs in the pipeline for

obstetric indications

uh this is another look at it and this

is a paper from

0

lets see where we 0 so this is a

new paper

looking at the cost or the trial number

comparing

trials of

medications for preterm birth against

breast cancer

preeclampsia against lung cancer and

preeclampsia against inflammatory bowel

disease and you can see that in terms of

the cost on the left side the incidence

of lung cancer and inflammatory bowel

disease the incidence is actually pretty

similar

however theres a really gross in

difference between the number of

trials for preterm birth preeclampsia

with compared with lung cancer and

preeclampsia with inflammatory bowel

disease and in some ways this does in

fact reflect the previous slide that

showed that there were vanishingly few

new drugs being

developed for obstetric indications

okay id next like to talk about

physiologic and pharmacologic changes

during pregnancy

this is a slide showing the

changes in hormonal concentrations

during the period of gestation and you

can see the

beta hcg estradiol progesterone which

are all increasing during pregnancy as

well as relaxant so you can see that

this is a very

scientifically medically

hormonally complex

situation during pregnancy

these are examples of physiologic

changes in pregnancy and essentially

whats going on in pregnancy is this is

a sort of a physiologic stress test

during the nine months of gestation

so here we have first of all the

percentage change in cardiac output

stroke volume and heart rate and again

heart rate time stroke volume is cardiac

output and you can see that even

very early in the pregnancy during the

first trimester there is a dramatic

increase in cardiac output

in terms of maternal intravascular

volume changes again the same thing an

increase in total blood volume

plasma blood volume and so on

there are also dramatic changes in

renal function and renal elimination

there is increased filtration

in part because of the increased cardiac

output going to the kidney

and there also

increases in the function of

transporters so these transporters are

moving drug actively from the

circulation into

the proximal tubule into the urine

in terms of glomerular filtration rate

and renal plasma flow in pregnancy again

as we saw with the increase in cardiac

output

the percentage change in glomerular

filtration rate and renal plasma flow

again increases dramatically very early

in the pregnancy and only after about

six to eight weeks of

birth

do the does the glomerular filtration

rate and renal plasma flow go back to

postpartum values

now you have to ask yourself

what is the clinical significance of

this this is a very interesting paper

by mary mary a bear from the university

of washington and her colleagues

a study was supported by the fda so

after 9

the postal service started receiving

packages of letters contaminated with

the anthrax

and the concern was how to treat the

people who were exposed to anthrax

and the question came up because of what

weve just seen in terms of renal

clearance

were the recommendations to treat

pregnant women exposed to anthrax with

amoxicillin

valid or not valid

and what you can see is

during the postpartum

as compared to the second and third

trimester

that the maximum concentration and the

area under the concentration curve in

terms of the exposure of amoxicillin was

significantly reduced in pregnant women

and the upshot of the paper was that

they did a series of modeling

experiments trying to figure out what

dose or what dosage interval

would be appropriate for treating

anthrax and the answer was none of them

so in other words anthrax cannot be

appropriately treated will not

appropriate will not be appropriately

treated with amoxicillin in pregnancy

okay this is the effect of pregnancy on

drug metabolism and gi motility and what

you can see here is that there are

increased activities in some of the

cytochrome

p0 enzymes and some of the

glucuronasal transferases

but decreased activity in others there

is also typically

decreased gastric emptying primarily

because of the mass of the uterus

now its possible to measure the

activity of those cytochromes using a

cocktail approach meaning that very

small amounts of active drugs

are given and then the concentrations

are seen over time in order to see the

specific activity of each individual

cytochrome midazolam is a marker for

cytochrome

[Music]

pa and what youre seeing is that

during pregnancy the concentrations of

midazolam are significantly decreased in

relation to

postpartum

times indicating again that the

cytochrome pa activity is

significantly increased in pregnancy

there have been other

situations where theres also been

concern about increased metabolism

during pregnancy and its clinical effect

so

uh during pregnancy theres a very high

mortality rate in pregnant women who

get the flu either influenza a or

influenza b

the treatment of choice for

those

infections is oseltamivir which is

tamiflu in the united states

so this study was done to compare

oseltamivir concentrations and its

active metabolite ocell tamivir

carboxylate in pregnant and nonpregnant

women and what you can see is a similar

curve pattern that the nonpregnant

women have have higher concentrations of

oseltamivir than the pregnant women now

the question you have to ask yourself is

should there be a dosage adjustment here

and theres been a lot of discussion

back and forth about whether its

necessary or not necessary so that is

that question is still out there however

just to let you know that the

pregnant versus the nonpregnant women

have a significantly different

area under the curve and drug exposure

for a drug to treat influenza

this is a recent paper that i thought

was quite interesting

at the moment there is an opioid

epidemic and

this was a study looking at

buprenorphine plasma concentrations

during pregnancy and postpartum again

showing a similar pattern

that in the first and second trimester

the concentrations of buprenorphine

which is used to treat women to avoid

them going into narcotic or opioid

withdrawal

are significantly lower than they are in

postpartum and the issue here is that

the last thing you want a pregnant woman

to do is to go into opioid withdrawal

this is a disaster for her health its a

disaster for fetal health and so the

question that needs to be posed as an up

followup to this study is should the

dose or the dosage interval be adjusted

for women who are pregnant who require

buprenorphine to avoid opioid withdrawal

okay so thats some information about

pharmacokinetics now the next question

you have to ask yourself is

what are the pharmacodynamic changes

that accompany the pharmacokinetic

changes during pregnancy and these are

some nice

uh papers that were summarized by uh

visca and jusco

about 0 years ago

looking at

differences in heparin

and its pharmacodynamic

outcome of change in

activated partial thromboplastin time

in pregnant and nonpregnant women and

nifedipine and what youre seeing in

these plots is that

in

the above

slide the nonpregnant women have much

higher

heparin concentrations than the pregnant

women

and also in the second

in b you can see that the active partial

thromboplastin time is significantly

higher in other words theres a stronger

response in the nonpregnant versus the

pregnant women

in the lower panel youre seeing

nifedipine concentrations against

changes in systolic blood pressure

in the yellow section of the

nonpregnant and in b in the postpartum

and again youre seeing the same sort of

pattern where theres a decreased

concentrations of nithypine in the

pregnant population as well as the

significantly decreased pharmacodynamic

response of a drop in blood pressure

now when youre talking about pregnancy

were talking about the mother but were

also talking about the fetus so in terms

of fetal drug transfer which were going

to get to now

the concern is over the three trimesters

of pregnancy so in first trimester

theres embryogenesis and organogenesis

and this is the time that tends to be

most sensitive to

uh drugs and specifically terratogenic

potential of medications

in the second trimester theres fetal

maturation and growth which is even more

dramatic in the third trimester where

theres increased

again fetal maturation and fetal growth

so how does drug get transferred from

the maternal compartment into the fetal

compartment so on the left side of this

picture

is the fetus head down the umbilical

cord

and the placenta

which you can see is a blow up on the

right so this is a blow up of the

placenta

and you can see the mothers blood

vessels

the fetal blood vessels and then the

space in between and the space in

between is where the

drug is being transported or diffused

across the maternal circulation to the

fetal circulation

and back again

so this is my

rudimentary

picture of whats going on here so we

have the maternal compartment on the

right the placenta in the middle and the

fetal compartment on the left

and we have diffusion

so some compounds diffuse back and forth

you can see the arrows going from the

maternal to the fetal compartment and

back again

and the diffusion takes place depending

on some characteristics of the drug

its also related to the blood flow

theres an increase in blood flow to the

placenta to the fetal compartment as the

gestation continues but in terms of the

drug

[Music]

properties

lipid solubility molecular weight

protein binding and ionization affect

the ability of drug to go from or to

diffuse between one compartment and the

other so drugs that are very lipid

soluble for example opioids will flow

freely between the maternal and fetal

compartments

high molecular weight compounds will not

move as easily highly proteinbound

compounds will not move as easily and

drugs that are ionized tend to not move

as freely either

in addition to diffusion theres also

active transport from the placenta to

the fetal compartment and active counter

transport

from the placental compartment back to

the maternal compartment

in terms of fetal exposure

the fetus is continuing to grow during

the gestation with increase in kidney

function increase in liver function so

ability to metabolize the drug through

the liver

the ability to renally excrete the drug

through the kidney and changes in the

diffusibility of the drug going into the

brain because the bloodbrain barrier

also has these sorts of barriers of

active transport active counter

transport

okay so again just to reiterate fetal

drug exposure is related to the

placental transport and counter

transport functions as well as kidney

function

hepatic function and the maturity of the

bloodbrain barrier

this is very interesting so i didnt
know about this journal of visualized
experiments but this is a picture of the
human placental perfusion model
so if you want to see in an in vitro way
what compounds are going from the
maternal circuit into the fetal circuit
you can obtain
after the consent of the mother the
human placenta and actually have it
being perfused by
fluids in the maternal compartment going
through the placenta into the fetal
compartment and if you look at this
website its very interesting because
the the um the pi explains really nicely
how to set up the experiment and so on
and this has become very useful because
one of the questions you want to know is
if youre giving a woman a drug during
the pregnancy is it going to get to the
fetal compartment and is that good or
not good if its chemotherapy you
probably dont want it to go to the
fetal compartment but there are
situations where you actually want to

treat the fetus through the maternal

circulation and so in this way you can

actually see whats going through the

placenta and back again

okay so

again in addition to the diffusion of

the drugs going back and forth there are

all these series of transporters that

are responsible for efflux for example

the mrp

is an eflux transporter

bcrp is an efflux transporter and all

these other

transfer races are influx transporters

so in addition to the diffusion there

also active

transport going on pushing the drug

either toward the fetal compartment or

back to the maternal compartment

and where this has become very helpful

again is in terms of setting up

clinical trials to pick drugs which

either

will will go through the placenta if

thats what you have in mind to treat

the fetus or drugs that will stay in the

maternal compartment

so this is a study of pravastatin

this is one of those maternal conditions

its induced by pregnancy and its

called

preeclampsia

eclampsia is actually

seizures caused by very high blood

pressure in the

mother

preeclampsia is a condition where the

blood pressures are elevated and it

seems to be caused although its not

exactly clear by endothelial damage and

inflammation

and pravastatin which was initially

developed to reduce blood cholesterol

also has the properties of reducing

inflammation and treating this

endothelial dysfunction

so after using this placental perfusion

model to determine whether pravastatin

would actually cross into the fetal

compartment from the maternal

compartment and many months of

discussion with the food and drug

administration it was determined that

under eye investigational new drug

application a study could go forward

comparing placebo to 0 milligrams of

pravastatin for women

who had previously experienced

preeclampsia

and where it was desirable to prevent

preeclampsia

and you can see that these results are

pretty clear

maternal outcomes

preeclampsia in the placebo group

there were four of them

in the pravastatin group zero

severe features of preeclampsia three in

the placebo group zero in the

pravistatin group so this is a practical

application of the use of the

placental perfusion model

so our research questions about

placental function include how does

placental function change during

pregnancy

how is placental function affected by

disease such as gestational diabetes

mellitus preeclampsia and so on and how

can these questions be addressed safely

by noninvasive methods and what is the

role of animal models again i dont have

any answers for these questions but they

certainly are research questions that

come up

okay next i wanted to talk briefly about

fetal pharmacokinetic pharmacodynamic

changes during gestation again these are

sort of hard to get at

renal function at birth is very low the

creatinine clearance or excuse me the

glomerular filtration rate is typically

about

0

of the adult value

hepatic phase enzymes

are typically extremely low

at birth

and fetal hepatic phase enzymes for

example

for glucuronidation are also extremely

low

the practical application of this has to

do with chloramphenicol so

chloramphenicol has been around since

the 90s

and in 99 there was an interesting

paper in the new england journal showing

that there was an increased mortality

rate

in preterm infants

who had prolonged uh rupture of

membranes

who were treated with chloramphenicol

and what they figured out was that this

extremely low amount of glucuronidation

low renal function

had actually been the cause of these

deaths these gray baby deaths so there

is the practical application of of

why its important to recognize that

fetal hepatic function renal function is

very low and that there need to be

dosage adjustments made for

neonates particularly preterm neonates

when theyre being treated with

medications

okay next i wanted to talk about

maternal treatment for a fetal condition

and i wanted to start with uh

supraventricular ventricular tachycardia

so svt is a its a fairly rare condition

um but it can lead to fetal death if the

heart rate is not controlled

the fetus will go into heart failure and

die

so i wanted to point out a couple of

things so first of all it is possible to

treat a fetus for a fetal condition

using the mother as sort of the vehicle

to transmit the drug

this study was done actually over the

course of 0 years it was published in

0

but the data collection in a

nonrandomized fashion so this was not a

randomized controlled trial this was

just uh standard of care

showed that the women who receive

flechanide

showed a better fetal response in terms

of decrease in heart rate than the

digoxin or the sodalol arms

and another example of using the mother

to transmit drug to the fetus is the

issue of

preterm labor and

decreased pulmonary function and

decreased surfactant production in

preterm infants and i thought this was

a quite interesting

trajectory of

scientific thoughts so 9

influence of pituitary adrenal system on

the differentiation of phosphatase and

the duodenum of the suckling mouse okay

9 we moved to fetal rabbits

and then the

very wellknown paper by the liggins

group about fetal lambs infused with

glucocorticoids

and the theory that there perhaps was

induction of accelerated appearance of

surfactant activity okay so thats that

brings us to 99

0 the american college of obstetrics

and gynecology puts out a position

opinion on the use of antenatal

corticosteroid therapy for fetal

maturation which has clearly become the

standard of care a single course of beta

methazone is recommended for pregnant

women between and 0s weeks and

and weeks of gestation at risk of

preterm birth within seven days and who

have not received a previous course of

antinatal corticosteroids

and this unfortunately is the drug label

for beta methazone so despite the fact

that there have been five or six decades

worth of research on the use of

antenatal corticosteroids either

dexamethasone or betamethazone

to induce surfactant production

there is certainly a lag in the drug

labeling

i wanted to talk briefly about drugs and

breast milk um

drugs and other substances transferred

from maternal circulation to breast milk

are transferred by diffusion and active

transport mechanisms so if you refer

back to the slide about the placenta

these are the same kinds of

manner through which drugs go into

breast milk lipid solubility the more

lipid soluble the drug

the more likely it will end up in breast

milk

protein binding again drugs that are

highly protein buying will probably not

wind up in breast milk molecular weight

larger molecular weight compounds will

not be uh

transferred into breast milk and drugs

that are ionized also will not transfer

very well into breast milk but there are

also active transport mechanisms similar

as we saw in the liver

in the kidney in the placenta

now what i wanted to point out here was

that the amount of drug thats ingested

by the

the breastfeeding infant is equal to the

concentration of the drug in the breast

milk times the volume this is a standard

equation

however the amount of the drug ingested

in other words swallowed by the infant

is not the amount of drug absorbed and

the amount of drug absorbed has to do

with the

maturity of the intestinal end of the

epithelium excuse me the hepatic

metabolism in other words as the

neonate becomes an infant the hepatic

metabolism picks up and so therell be

increased metabolism

and

less drug exposure and also renal

clearance

the reason i bring this up is theres

been a lot of

news about the use of codeine in

breastfeeding and the very specific

issue here is that

codeine and other narcotics are

metabolized to morphine thats how they

work

however there have been occasional rare

but unfortunate cases where the mothers

had a sip d ultra rapid

rapid metabolizer genotype

where the mother instead of

metabolizing lets say 0 percent of the

codeine to morphine was suddenly

metabolizing 0 percent or 0 or 0

percent of the codeine to morphine and

this is created uh sedated infants

there have been a couple of rare cases

of infant fatalities

so i just wanted to point out that there

there are issues around coding and the

rare but

serious cases of

ingestion of increased amounts of

morphine in

sip d six ultra rapid metabolizers

so in terms of our research questions

for fetal pharmacokinetics

pharmacodynamics and pharmacogenomics

are how do fetal pharmacokinetics change

and by what mechanisms throughout

gestation and how would you be able to

figure that out

how do fetal pharmacodynamics change and

by what mechanisms during gestation

and what are the fetal pharmacogenomics

which affect the pharmacokinetics and

the pharmacodynamics

the other question is what happens when

there is illness when there are medical

conditions so how do maternal or fetal

conditions affect fetal pharmacokinetics

pharmacodynamics pharmacogenome genomics

fetal reprogramming and what are the

longterm effects on growth and development

how can fetal pharmacology be studied safely and noninvasively throughout gestation and what is the role of animal models

how can medicines be developed for fetal conditions

and what short and longterm outcome measures should be considered in drug development

in terms of drug exposure in the embryo and the fetus and the infant what is the exposure what is the risk of the exposure are we worried are we not worried

during what embryonic or fetal period is the exposure occurring

what are the short and longterm consequences of this drug exposure

and if the mother does not treat her medical condition because of concern of infant exposure what are the short and long term consequences for the mother and the infant again these are very complicated questions but i i think that

they should be raised

now

a lot of the underlying issue about the

lack of drug development

or

drug treatment for the pregnancyinduced

conditions that we talked about in the

first couple of slides are the issue of

druginduced birth defects

this is a paper from 0 showing the

baseline rate of fetal malformations now

they werent corrected for anything but

at baseline in the united states theres

about a three percent

uh congenital malformation rate at

baseline

but what no one wants to repeat is two

complete disasters the first one was

druginduced birth defect by thalidomide

it was developed for nausea and vomiting

of pregnancy

it was marketed originally in germany in

90

the off target effect was blood vessel

angiogenesis growth inhibition

and the toxicity was focomelia so we see

this beautiful little girl

with no arms and thats the one thing

that nobody wants to repeat because the

uh the animal studies showed no toxicity

but then you wind up with human toxicity

another example diethylstilbestrol des

the indication was for prior pregnancy

loss on the theory that if you increase

the mothers estrogen concentrations

the

chance of pregnancy loss would decrease

this was marketed between 90 and 9

and it was in the cattle feed supply in

the us through the 90s the offtarget

effect was as an endocrine disruptor and

the toxicity came out about 9 when

there were these odd reports of vaginal

clear cell carcinoma which was

vanishingly rare but suddenly was

increased

and after looking around to figure out

what the causative agent could be it

seemed that a lot of the

the women that were presenting with

these vaginal clear cell carcinomas

their mothers had received des during

their pregnancy

however this also causes urogenital

anomalies in boys

and

even though in humans theyve been

looking into the second generation just

because of the timing for this in the

rodent model these

abnormalities are still continuing

through the third generation in rodents

and it remains to be seen whether this

will continue in humans as well

this is a slide about acog

recommendations for chronic hypertension

in pregnancy and i wanted to point out

two things um the first one is that

methyl dopa which is uh listed third on

common oral antihypertensive agents in

pregnancy uh lists methyldopa

methyl dopas been around since probably

the 90s maybe earlier than that

its main advantage is that it appears to

be safe and doesnt seem to cause any

congenital anomalies however one of its

major side effects is

depression which is not a desirable

effect in pregnancy

the other thing i wanted to point out is

that on the bottom on the left the

angiotensin converting enzyme inhibitors

and the angiotensin receptor blockers

are associated with fetal anomalies and

contraindicated in pregnancy and the

preconception period

however the reason that we know this is

because of postmarketing studies and

epidemiologic studies so it would have

been nice to know in a more

mechanistic toxicology fashion that

these were going to be potential

problems

questions to consider in obstetric drug

development include what is the clinical

condition in the pregnant woman that

requires treatment

is there a condition during pregnancy

mechanistically similar to a condition

occurring outside of pregnancy

in other words is preeclampsia similar

to hypertension because

thats how its being treated for the

most part is gestational diabetes

mellitus similar to type diabetes

mellitus and its preterm labor similar

to an asthma attack because theyre both

being treated with beta agonists so

clearly if preterm labor is not

an asthma attack it would be nice to

have other drugs being developed for

this

indication is there sufficient basic

science research investigating the

disease mechanism i would probably argue

no

has the basic research provided any drug

targets and is the pregnant woman the

same as a nonpregnant woman in terms of

drug concentration time course and drug

effect and i think weve seen over the

last bit that that is not the case

so the research needs in this area are

many

theres a lack of basic science on

disease mechanisms in pregnancy

theres a need for basic science on

placental and breast milk drug transport

theres a lack of mechanistic approach

to preclinical toxicology and

offtarget effects of drugs

so lack of developmental of development

excuse me of novel drug targets

applicable to pregnancy and lactation

including development of placental drug

transporter inhibitors

there is a need for a better

understanding of placental transport and

counter transport with novel ways of

assessing immature placental function

this is especially an issue because

most of the information we have about

placental function is on the fullterm

placenta

and also on a fullterm healthy placenta

uh there is a need for meaningful

feasible validated accepted shortterm

and longterm clinical trial outcome

measures that was reflective in the

study of treatment of svt in the fetus

where that was not a randomized

controlled trial and took 0 years to

accrue the number of patients that they

did for publication

and theres a need for improved

feasibility of clinical trial designs in

pregnancy to allow more pregnant women

and lactating women to be enrolled in

clinical trials

thank you very much for your attention

and i appreciate any questions or

discussion you may have feel free to

contact me at any time thank you very

much

you