

# More Than Just a Cough: Exploring the Role of the Cytoskeleton in Fertility

by

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## Part I – Medical History

Dr. Martin Aguilar began his first day of residency in the fertility clinic with nervous excitement. After four years of medical school, he was eager to finally begin his career, and he was thrilled to be working under the esteemed Dr. Petrova at the Vermont Center for Reproductive Health. Dr. Aguilar had spent the weekend reviewing all of his notes about human reproduction and watching videos showing the details of specific events.

*Watch this video about the process of fertilization:*

<https://youtu.be/Vv9Kj3XIAbU>

Before meeting their first patients of the day, Drs. Aguilar and Petrova sat down and reviewed the nurse's notes about the couple's medical history.

### Case File B273

*Summary: Julia and Robert Buckley; requested an appointment to assess fertility; tried to conceive for 22 months with no success*

**Julia Buckley** Age: 31 years Height: 67 in Weight: 142 lbs

Regular menstrual periods, cycle length 29 days, flow medium

First menstrual period at age 13

Prior pregnancies: 1 Live births: 0

*Notes: 5 years ago - unplanned pregnancy; at 9 weeks gestation was found to be ectopic (occurring outside of the uterus, typically in the fallopian tube), surgical removal of left fallopian tube containing embryo, no damage to surrounding tissue.*

**Robert Buckley** Age: 32 years Height: 72 in Weight: 176 lbs

Prior pregnancies: 1 (with Julia Buckley, described above)

Normal erectile function, no history of injury to testes

*Notes: Asthma, typically brought on by allergies*

*Questions*

1. List any details from the medical history of Robert and Julia that may warrant consideration as you explore the cause of their infertility.
  
2. As you are reading the rest of this case study, keep in mind what you have learned about the cytoskeleton, as it will be important to solving the case. Refer back to the video or your textbook for information and then complete the table below to organize information about the structure and function of the three types of cytoskeletal elements found in eukaryotic cells. In the last column, list at least one way that each type of cytoskeletal element is involved (either directly or indirectly) in fertility.

	<i>Structure</i>	<i>Functions</i>	<i>Fertility</i>
<i>Microtubules</i>			
<i>Microfilaments</i>			
<i>Intermediate Filaments</i>			

## Part II – Meeting the Buckleys

As Robert and Julia Buckley entered Dr. Petrova’s office, they unlocked their hands to reach out to the doctors’.

Robert began, “Pleased to meet you, Dr. Petrova. And you, Dr...”

“Aguilar. I am a new associate in the practice.”

“Hello, Dr. Aguilar,” smiled Julia.

“Please, have a seat. Let’s talk about why you are here with us today,” Dr. Petrova offered graciously. “We have reviewed the history that you gave the nurse, and I see some good signs here. You are having regular periods, which means you are likely ovulating normally. And you have conceived in the past.”

“Well, conceived, yes, but it didn’t work out so well,” Julia noted.

Dr. Aguilar responded, “I see that. Ectopic pregnancies, when the embryo implants somewhere other than the uterus, are not actually so uncommon. They occur in just under 2% of pregnancies. And your surgical report showed that besides losing a fallopian tube, the surgery was successful. The good news is that means that you were both physically able to conceive, at least a few years ago. We will certainly do some tests to see where you stand now. The down side is, unlike other women who have the opportunity for pregnancy with each ovulation, half of your ovulated eggs aren’t available for fertilization since the left fallopian tube is not present for the sperm to enter.”

“Of course. So it’s no surprise that we might take a little longer to get pregnant. But we’ve been trying for almost two years! I’m starting to worry that something more is wrong,” Robert said, his brow furrowing with tension.

“And we will do our best to find out if that is true,” Dr. Aguilar said.

“Thank you, Dr. Aguilar,” Julia said, reaching over for her husband’s hand. “Where do we begin?”

“Well, because of your anatomical differences, assessing causes of infertility in women is much more invasive than it is for men, so we always start by examining a sperm sample. In a moment, we will send you up to the collection room, Mr. Buckley, and then our laboratory technicians will examine your sample. They will perform a count to be sure that you are producing enough sperm, take a look at their structure to be sure that they look healthy, and measure their motility. They have a tough journey in order to make it all the way up to the fallopian tubes, so we want to be sure they are good swimmers!” Dr. Aguilar chuckled, trying to lighten the tension in the room. “The results will come back in just a few hours, and we will give you a call to let you know what was observed.”

“I’m sure everything will be fine, honey,” Julia said to Robert. Looking back to Dr. Aguilar, she asked, “So if that all comes back good, then what happens next?”

“Then we will take a closer look at you, Julia,” Dr. Aguilar replied.

### Questions

3. Which of the three types of cytoskeletal elements (microfilaments, microtubules, and intermediate filaments) are present in a sperm cell? What would be the impact of a loss of function in each of the types of cytoskeletal structures?

	<i>Present in sperm cells? (Yes/No)</i>	<i>Loss of function</i>
<i>Microtubules</i>		
<i>Microfilaments</i>		
<i>Intermediate Filaments</i>		

4. Julia had an ectopic pregnancy a few years ago, where the embryo remained in the fallopian tube instead of traveling to the uterus. Which cytoskeletal structure is involved in the movement of eggs or embryos down the fallopian tubes?

## Part III – Test Results and New Questions

Julia and Robert were having lunch when the phone rang later that day, and Robert sprang up to answer it.

“Hello?”

“Hi, Robert, this is Dr. Aguilar- is this a good time?”

“Sure, doctor, what’s the verdict?”

“*The analysis of your sperm came back fine. Your counts were well within the normal range, morphologically they look normal, and they scored very high on the motility measurement. You have perfectly healthy sperm.*”

“Well that is great... for me. But what does this mean for Julia?”

“*We would like to have you both come back in to talk about next steps, but Julia will need to have some testing done as well. I’ll connect you to the front desk, and they can set up an appointment.*”

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A few days later, Robert and Julia were back at the clinic. They headed back into the office and sat down across from Dr. Aguilar, who had a stack of notes and procedure forms waiting to be signed.

Dr. Aguilar began, “Okay, Julia, since we know that Robert’s sperm are healthy, we’re ready to explore some possible issues with you. One of the...”

*Cough cough cough.* “Oh, excuse me, Dr. Ag-,” *cough cough* “I’m sorry. Robert, can you pass me the water?” Julia gasped to catch her breath, reaching for the water bottle from Robert.

“Asthma acting up?” Dr. Aguilar asked. “Wait, Robert, you’re the one with asthma, right?” Dr. Aguilar shuffled through his notes.

“Yes, I’ve had asthma since I was a kid. Julia just has sensitive lungs, I guess. She’s always coughed a lot,” Robert explained as Julia coughed again and took a drink.

Julia cleared her throat, “I went to a bunch of doctors when I was younger, and I’ve had x-rays, allergy tests, and measurements of my lung function, but no one has ever found a reason for the cough. I’ve just gotten used to it, so I stopped trying to fix it.”

Dr. Aguilar paused and stared up at the ceiling, deep in thought. Then he looked back down at his desk and started flipping through his notes again. “Julia, when you had your surgery, do you know if someone took a sample of your fallopian tube?”

“Um, I don’t think so, Dr. Aguilar. No one ever told me they did,” Julia responded, puzzled about why this question was coming up now. “Why would you want to see it?”

Dr. Aguilar explained, “I’m just wondering if there is a connection between your cough and the ectopic pregnancy.”

Robert cocked his head to the side and furrowed his brow, “How would that be related?”

### Questions

- How *would* they be related? What hypothesis is Dr. Aguilar working from to explain the connection between Julia’s cough and her ectopic pregnancy? (*Hint*: What cytoskeletal element is present in both lungs and reproductive organs?)
- Dr. Aguilar wanted to see the fallopian tube that was removed. Since it wasn’t retained, from what other tissue might Dr. Aguilar be able to take a sample to explore his hypothesis? (Taking a sample from the remaining fallopian tube is not a good option, as it is an invasive procedure and may further negatively impact her fertility.)

## Part IV – Finding Answers

Dr. Aguilar walked into Dr. Petrova's office and lay open a folder on her desk. "I figured it out!" he shouted excitedly. In front of them were two images—one from an individual with normal cilia, and another from a biopsy he ordered of the lining of Julia's sinuses.

"Great, Martin, now tell me what I am looking at here," said Dr. Petrova.

Dr. Aguilar explained, "Okay, what you are looking at are cross sections of normal and abnormal cilia. Cilia and flagella are made up of microtubules, long chains of tubulin proteins that provide structure and sometimes motility. You see, some cilia are motile and some are non-motile, used instead as sensory organelles. Anyway, in a normal motile cilium, there are 9 pairs of microtubules, arranged in a circle, with 2 individual microtubules in the middle. This is called the 9+2 arrangement. You can see that clearly in the photo on the left, labeled 'control.' That sample was taken from someone with normal ciliary function. This arrangement is really important, and it allows the cilia to bend and move properly.

"But there is a genetic disorder, called Primary Ciliary Dyskinesia, that alters the structure of cilia. Sometimes other proteins in the cilia are affected, and sometimes it's the arrangement of the microtubules that is changed. On the right you can see what Julia's cilia look like. She has the normal 9 pairs going around the circle, but she is missing the 2 microtubules in the middle! That's called a 9+0 arrangement, and it means that her cilia can't move like they are supposed to. We took this sample from her sinuses because the respiratory tract is an easily accessible site of motile cilia."

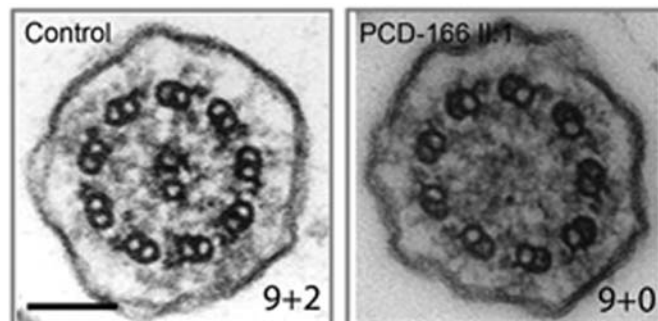
"So what made you think to check this out in the first place?" Dr. Petrova asked.

"When I saw her last week, she was coughing a lot and she explained that she has had this chronic cough all her life. Cilia are very important in the respiratory tract for moving debris out of the lungs. If there is something wrong with the cilia, inhaled particles of dirt and bacteria can settle in the lungs, causing a chronic cough and sometimes severe lung infections. You know that cilia are also essential to fertilization and implantation of the embryo, because cilia lining the fallopian tubes move the embryo into the uterus. So this is likely why she had that ectopic pregnancy a few years ago. The sperm reached the egg and fertilized it, but the embryo couldn't make it out of the fallopian tubes. This probably also explains her infertility. Odds are, most of the eggs released from her ovaries never even make it to the fallopian tubes, as cilia at the end of the tubes are involved in catching the egg and bringing it into the tube in the first place."

"Great work, Martin," Dr. Petrova said with a smile. "Now Julia has a diagnosis for her infertility and her cough. And this means we know how to help the Buckleys conceive."

### Question

- Given all that you know about Julia and Robert's fertility, how might the doctors be able to help them conceive? What kind of reproductive assistance might be used?



*Figure 1: Transmission electron microscopy showing ciliary structure. The control panel (left) shows a cross section of a normal motile cilium, with a 9+2 arrangement of microtubules. The PCD (primary ciliary dyskinesia) panel (right) shows the absence of the central pair of microtubules. (Image credit: Crop of two micrographs from panel B of Figure 3 in: Onoufriadis, A., et al. 2014. Targeted NGS gene panel identifies mutations in RSPH1 causing primary ciliary dyskinesia and a common mechanism for ciliary central pair agenesis due to radial spoke defects. *Human Molecular Genetics* 23(13): 3362–3374. Open source article, CC BY 3.0.)*